PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 5/10, 5/08, 5/06, 5/02, A61K 38/55 | A1

(11) International Publication Number: WO 98/29435

(43) International Publication Date: 9 July 1998 (09.07.98)

(21) International Application Number: PCT/CA97/01004

(22) International Filing Date: 23 December 1997 (23.12.97)

(30) Priority Data:

60/034,041	27 December 1996 (27.12.96)	US
60/052,860	17 July 1997 (17.07.97)	US
60/059,806	23 September 1997 (23.09.97)	US

(71) Applicant *(for all designated States except US)*: BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100 Cunard, Laval, Québec H7S 2G5 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BAILEY, Murray [CA/CA]; 344 Groulx, Pierrefonds, Québec H8Y 1B3 (CA). FAZAL, Gulrez [CA/CA]; 955, rue Plymouth #411, Ville Mont-Royal, Québec H4P 1B2 (CA). LAVALLEE, Pierre [CA/CA]; 366 du Cheminot, Rosemère, Québec J7A 4B2 (CA). OGILVIE, William [CA/CA]; 335 rue Edgewood, Rosemère, Québec J7A 2M3 (CA). POUPART, Marc-André [CA/CA]; 101 Aimé-Seguin, Laval, Québec H7M 1B3 (CA).

(74) Agent: COTE, France; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA).

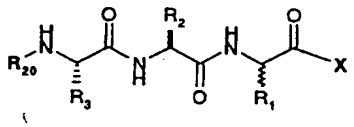
(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PEPTIDOMIMETIC INHIBITORS OF THE HUMAN CYTOMEGALOVIRUS PROTEASE



(I)

(57) Abstract

A compound of formula (I), wherein X is CF_3, C_2F_5, 2-benzothiazole, CF_2CONHR_6, $CONHR_6$, wherein R_6 is $CH_2C_6H_5$, CH_2(4-iodophenyl), CH_3, $(CH_2)_2OCH_2C_6H_5$, CH_2-2-benzimidazole, CH_2-(3,4-methylenedioxybenzene), $CH(CH_3)C_6H_5$ or $CH(CH_2CH_3)C_6H_5$; or X is 2-benzoxazole-R_7 wherein R_7 is H, 4-CH_3, 5-CH_3, 6-CH_3 or 7-CH_3; R_1 is H, CH_3 or CH_2CH_3; R_2 is CH_2CONH_2, $CH_2CH_2CONH_2$, CH_2-thiazole, $CH_2CON(CH_3)_2$, CH_2CO-(pyrrolidino), $CH_2CH(CH_3)_2$ or $CH_2C_6H_5$; R_3 is Et, $CH(CH_3)_2$, $C(CH_3)_3$, adamantyl, $CH_2C(CH_3)_3$ or $C(CH_3)_2CO_2H$; and R_{20} is $COCH_2C(CH_3)_3$, $COCH_2CH_2C_6H_4OH$, $COCH_2CH(CH_3)_2$, $CO_2C(CH_3)_3$, $CONHC(CH_3)_3$, $COCH_2N(CH_3)_2$, $CO(CH_2)_3CO_2H$, CO-(*S*)-$CH(NH_2)C(CH_3)_3$, CO-(*S*)-$CH\{NHC(O)O\text{-}C(CH_3)_3\}C(CH_3)_3$, CO-(*S*)-$CH\{NHCO(CH_2)_5NHC(O)OC(CH_3)_3\}C(CH_3)_3$ or CO-(*S*)-$CH\{NHCO(CH_2)_5NH_2\}C(CH_3)_3$. These compounds are useful for the treatment of human cytomegalovirus infection.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Peptidomimetic Inhibitors of the Human Cytomegalovirus Protease

Field of the invention

The present invention relates to compounds, composition and methods for the treatment of human cytomegalovirus (HCMV) infection. In particular, the present invention provides novel peptidomimetic inhibitors of the HCMV protease.

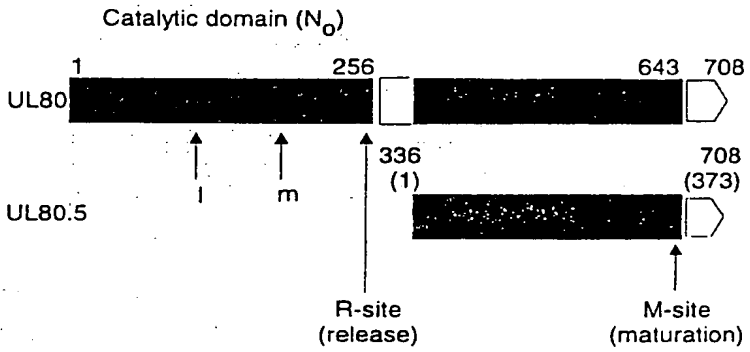
Background of the invention

The Human Cytomegalovirus (HCMV) is a highly prevalent member of the herpesvirus family infecting up to 80% of the general population. This virus is responsible for opportunistic infections in immunocompromised individuals including organ transplant recipients, cancer patients and AIDS sufferers. Clinical manifestations include disseminated disease, pneumonitis, retinitis and gastro-intestinal infections such as oesophagitis and colitis. Of particular significance are HCMV infections of neonates. This disease is the most common congenitally acquired viral infection in the world. It is estimated that 1% of newborn infants are infected and up to 10% of these are symptomatic and may experience severe complications. Mortality in this latter group approaches 30%.

All members of the herpesvirus family express a protein late in the virus life cycle which appears to function as a self assembling scaffold during the manufacture of the viral capsid. This assembly protein is present in immature B-capsids and must be processed to remove a short segment of the C-terminus in order to permit the entry of viral DNA and produce an infectious virus

particle. Recently it has been shown that this processing is mediated by a protease which is encoded by the virus. The protease itself is expressed as a precursor protein which is autocatalytically cleaved at least twice (Scheme 1). Cleavage occurs near the C-terminal end of the UL80 gene product (M-site) to remove a small fragment, and also at a position located near the center of the precursor (R-site) to excise the catalytic domain (N_o). Both N_o and the full length protease (UL80 gene product) are catalytically active.

Scheme 1



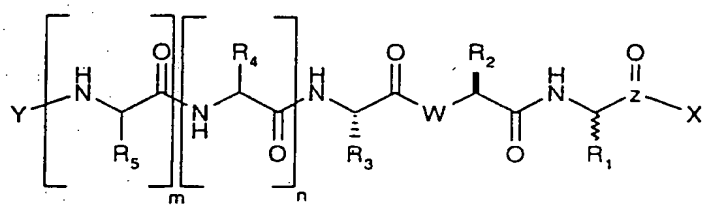
HCMV protease N_o shows significant sequence homology with other herpesvirus proteases. Affinity labeling experiments and site-directed mutagenesis indicate that this enzyme is a serine protease. Recent crystallographic results have shown that HCMV protease represents a novel structure of serine proteases and in fact possesses a unique catalytic triad.

While it has not been demonstrated that HCMV protease is absolutely required for viral replication, it has been shown that HSV-1 mutants lacking the analogous enzyme or expressing defective variations of it are unable to grow. The high degree of homology between the

proteases of HSV and HCMV support the idea that specific inhibitors of HCMV protease would show antiviral activity and thus have therapeutic value.

Summary of the invention

In accordance with the present invention, there is provided a compound of formula I:



(I)

wherein **z** is C or P;

when **z** is C, then **X** is CF_3; C_2F_5; benzothiazole; oxazolo[4,5b]pyridine; or benzoxazole-R_7 wherein R_7 is H or methyl;

or **X** is CF_2CONH-R_6, $C(O)NH$-R_6,

wherein R_6 is C_{0-10} alkyl optionally substituted with phenyl or cyclohexyl, said phenyl or cyclohexyl ring being optionally substituted with Me, halogen, $-CF_3$, -CH(Me)-C(O)-OBn; $-C(O)NH_2$; or -C(O)-morpholino; said phenyl or cyclohexyl ring optionally fused with a phenyl ring;

$(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-phenyl said phenyl optionally substituted with halogen;

$(CH_2)_{1-3}$-2-benzimidazole;

$(CH_2)_{1-3}$-(3,4-methylenedioxybenzene); or

$(CH_2)_{1-3}$-O-C(O)-$OCH_2CH=CH_2$;

or, when **z** is P, then **X** is $-(OPh)_2$;

R_1 is H, Me, or Et;

R_2 is $CH_2-SO_2NH_2$; $-C_{1-6}$ alkyl; $-(C_{1-6}$ alkyl) aryl; $-(C_{1-6}$ alkyl)thiazolo; $-CH_2C(O)-(C_{1-6}$ alkyl); $-CH_2C(O)-$pyrrolidino; $-CH_2C(O)-$morpholino; $-(C_{1-6}$ alkyl)amino; $-(C_{1-6}$ alkyl)amido optionally mono- or di-substituted with C_{1-6} alkyl, said alkyl optionally substituted with pyridino;

W is NH, CH_2 or $CH(CH_3)$;

R_3 is $-C_{1-12}$ alkyl; $-(C_{1-6}$ alkyl)C(O)OH; or adamantyl;

n is 0 or 1,
R_4, when n is 1, is $-C_{1-6}$ alkyl or $-(C_{1-6}$ alkyl)-aryl wherein said aryl is optionally substituted with OH;

m is 0 or 1,
R_5, when m is 1, is H or $-CH_2OH$;

and

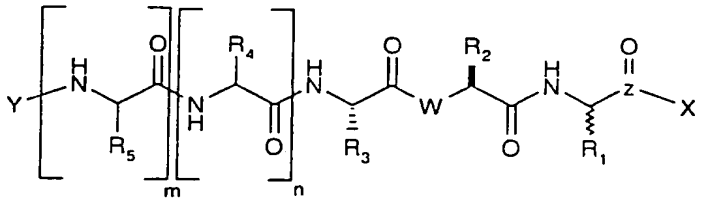
Y is H; $(CH_2)_2$-*t*-Bu; or an acyl of formula:
$-C(O)-(CH_2)_{1-6}-C(O)OH$;
$-C(O)-(CH_2)_{1-6}$ -Ph wherein Ph is optionally substituted with OH;
$-C(O)-CH_2N(CH_3)_2$;
$-C(O)-R_9$; $-C(O)O-R_9$; or $-C(O)NH-R_9$ wherein R_9 is C_{1-6} alkyl; or
$-C(O)-(CH_2)_{1-6}-NH_2$ wherein said amino group is optionally protected with an amino protecting group.

Included within the scope of this invention is a pharmaceutical composition comprising an anti-cytomegalovirus virally effective amount of a compound of formula I or a therapeutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier medium or auxiliary agent.

An important aspect of the invention involves a method of treating a cytomegalovirus viral infection in a mammal by administering to the mammal an anti-CMV virally effective amount of the compound of formula I or a therapeutically acceptable salt thereof, or a composition as described above.

Another important aspect involves a method of inhibiting the replication of cytomegalovirus virus by exposing the virus to a CMV protease inhibiting amount of the compound of formula I or a therapeutically acceptable salt thereof, or a composition as described above.

Preferred compounds of the invention include compounds of formula I:



(I)

wherein the substituents are defined below.

Preferably, z is C. or P.

More preferably, z is C.

Preferably, **X** is CF_3;
C_2F_5;
2-benzothiazole;
2-oxazolo[4,5b]pyridine;
2-benzoxazole-R_7, wherein R_7 is H, 4-Me, 5-Me, 6-Me, or 7-Me;
CF_2CONHR_6 or $C(O)NHR_6$ wherein
R_6 is C_{1-7} alkyl, optionally substituted with cyclohexyl, naphtyl, or phenyl
optionally substituted with Me, iodo, CF_3, -CH(Me)-C(O)-OBn; $-C(O)NH_2$, or -C(O)-morpholino;
$(CH_2)_2$-O-CH_2-phenyl;
CH_2-2-benzimidazole; or
CH_2-(3,4-methylenedioxybenzene);
or when **z** is P, then **X** is $(OPh)_2$.
More preferably, **X** is CF_3;
C_2F_5;
benzothiazole;
benzoxazole-R_7, wherein R_7 is H, 4-Me, 5-Me, 6-Me, or 7-Me;
$-CF_2CONH-CH_2$-phenyl;
$-C(O)NHR_6$ wherein
R_6 is $-CH(Me)(CH_2)_4CH_3$; cyclohexyl; naphtyl; $-CH_2$-phenyl; $-CH(CH_3)$-phenyl; or $-CH(CH_2CH_3)$-phenyl; ; $-CH_2$-4-iodophenyl; -phenyl-CH_3; -phenyl-CF_3; -phenyl-$C(O)NH_2$; -phenyl-C(O)-morpholino; -phenyl-CH(Me)-C(O)-OBn; $-(CH_2)_2$-O-CH_2-phenyl; $-CH_2$-2-benzimidazole; $-CH_2$-(3,4-methylenedioxybenzene); or $-(CH_2)_2$-O-C(O)-$OCH_2CH=CH_2$;
or when **z** is P, then **X** is $(OPh)_2$.
Most preferably, **X** is C_2F_5;
$-C(O)NHR_6$ wherein

R_6 is $-CH_2$-phenyl; $-CH_2$-4-iodophenyl; $-CH(CH_3)$-phenyl; or $-CH(CH_2CH_3)$-phenyl; -CH(Me)-naphtyl; $-CH_2CH(Me)$-phenyl; $-(CH_2)_2-O-CH_2$-phenyl; $-CH_2$-2-benzimidazole; or $-CH_2$-(3,4-methylenedioxybenzene);

Preferably, R_1 is H, methyl or ethyl.
More preferably, R_1 is H or methyl.
Most preferably, R_1 is H or methyl;

Preferably, R_2 is $-CH_2$-phenyl;
$-CH_2$-(4-thiazolo);
$-(CH_2)_{1-4}-NH_2$;
$-CH_2-C(O)$-*tert*-butyl;
$-CH_2-C(O)$-(N-pyrrolidino);
$-CH_2-C(O)$-(N-morpholino);
$-CH_2SO_2NH_2$;
$-(CH_2)_{1-2}$-amido, the nitrogen of said amido optionally mono- or di-substituted with a substituent selected independently from: CH_3; *t*-Bu; phenyl; or $-CH_2CH_2$-(2-pyridino).
More preferably, R_2 is $-CH_2-C(O)$-(N-pyrrolidino);
$-CH_2-C(O)$-(N-morpholino);
$-CH_2SO_2NH_2$;
$-(CH_2)C(O)NH_2$;
$-(CH_2)_2C(O)N(CH_3)_2$;
$-CH_2-C(O)-NH-t$-Bu; or
$-(CH_2)_2-C(O)-N(CH_3)CH_2CH_2$(2-pyridino).
Most preferably, R_2 is $-CH_2-C(O)$-(N-pyrrolidino);
$-CH_2-C(O)$-(N-morpholino);
$-(CH_2)_2C(O)N(CH_3)_2$; or
$-(CH_2)_2-C(O)-N(CH_3)CH_2CH_2$(2-pyridino).

Preferably, W is NH or CH_2.

More preferably, W is NH.

Preferably, R_3 is ethyl; isopropyl; *t*-Bu; CH_2-*t*-Bu; or adamantyl.
More preferably, R_3 is ethyl; isopropyl; or *t*-Bu.
Most preferably, R_3 is isopropyl; or *t*-Bu.

Preferably, **n** is 0 or 1.
More preferably, **n** is 0.
Alternatively, more preferably, **n** is 1.

Preferably, R_4, when **n** is 1, is isopropyl; *t*-Bu; or 4-hydroxybenzyl.
More preferably, R_4, when **n** is 1, is isopropyl; or *t*-Bu.
Most preferably, R_4, when **n** is 1, is *t*-Bu;

Preferably, **m** is 0 or 1.
More preferably, **m** is 0.

Preferably, R_5, when **m** is 1, is H.

Preferably, **Y** is H; $-CH_2-CH_2-t$-Bu; or an acyl of formula:
$-C(O)CH_3$;
$-C(O)CH_2-CH(CH_3)_2$;
$-C(O)CH_2-t$-Bu (DA-Tbg);
$-C(O)(CH_2)_2$-4-hydroxyphenyl;
$-C(O)-(CH_2)_3-COOH$;
$-C(O)O-t$-Bu (Boc);
$-C(O)NH-t$-Bu;
$-C(O)CH_2-N(CH_3)_2$; or
$-C(O)(CH_2)_{1-6}NH_2$, said amino group optionally protected with an amino protecting group.

More preferably, **Y** is H; or an acyl of formula:
-C(O)CH_3;
-C(O)CH_2-CH(CH_3)$_2$;
-C(O)CH_2-*t*-Bu (DA-Tbg);
-C(O)(CH_2)$_2$-4-hydroxyphenyl;
-C(O)-(CH_2)$_3$-COOH;
-C(O)O-*t*-Bu (Boc);
-C(O)(CH_2)$_5NH_2$; or
-C(O)(CH_2)$_5$NH-Boc.

Most preferably, **Y** is an acyl of formula:
-C(O)CH_2-*t*-Bu (DA-Tbg);
-C(O)O-*t*-Bu (Boc);
-C(O)(CH_2)$_5NH_2$; or
-C(O)(CH_2)$_5$NH-Boc.

A preferred compound of the invention is selected from the group consisting of:

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-2-methyl-1-[((1*S*)-2-methyl-1-[(methylcarboxamido)methyl] carboxamidopropyl) carboxamido]propylcarboxamido) butanediamide (**37**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-6-amino-2-((1*S*)-1-[((1*S*)-1-[(1*S*)-2-hydroxy-1-(methylcarboxamido) ethyl]carboxamido-2-(4-hydroxyphenyl)ethyl)carboxamido]-2-methylpropyl-carboxamido)hexanamide (**38**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamidopropyl) carboxamido]butanediamide (**39**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-{(1*S*)-2-methyl-1-[(methylcarboxamido)-propyl]carboxamido}butanediamide (**40**);

*N*1-(3,3,3-trifluoro-(1*S*)-methyl-2-oxopropyl)-(2*S*)-2-{(1*S*)-2-methyl-1-[(methylcarboxamido)propyl]carboxamido}butanediamide (**43**);

*N*1-(1-ethyl-3,3,3-trifluoro-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl)carboxamido]butanediamide (**44**);

*N*1-(1-(3,3,3,-trifluoro-1-propyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methyl-carboxamido)propyl]carboxamidopropyl)carboxamido]butane diamide (**45**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl)carboxamido]pentanediamide (**46**);

(3*S*)-3-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido-propyl)carboxamido]-3-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]propanoic acid (**47**);

*N*1-[(1*S*)-1-((1*S*)-2-hydroxy-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)-2-methylpropyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**48**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-6-amino-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]hexanamide (**49**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-2-(1,3-thiazol-4-yl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)-carbamoyl]ethylcarbamoyl) propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**50**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]butanediamide (**51**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-4-methyl-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]pentanamide (**52**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-2-phenyl-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-ethylcarbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**53**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-2-methyl-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-propylcarbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**54**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**55**);

*N*1-[(1*S*)-2-methyl-1-((1*R*)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**56**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]butanediamide (**57**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2,2-dimethyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido-propyl)carboxamido]butanediamide (**58**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-3,3-dimethyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido butyl)carboxamido]butanediamide (**59**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((*S*)-1-(1-adamantyl)-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido methyl)carboxamido]butanediamide (**60**);

(3*S*)-3-((1*S*)-2-(dimethylcarbamoyl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-ethylcarbamoyl)-2,2-dimethyl-3-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropanoic acid (**61**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(methylcarboxamido)propyl]carboxamidobutanediamide (**62**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-1-[(4-hydroxyphenethyl)carboxamido]-2,2-dimethylpropylcarboxamido) butanediamide (**63**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-1-(isobutylcarboxamido)-2,2-dimethylpropyl]carboxamidobutanediamide (**64**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamidobutanediamide (**65**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-1-[(3,3-dimethyl-butyl)amino]-2,2-dimethylpropylcarboxamido]butanediamide (**66**);

4N,4N-Dimethyl-1N-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-2-[1-(*tert*-butoxycarbonyl-amino)-2,2-dimethyl-(1S)-propylcarboxamido]-(2S)-butanediamide (**67**);

N4,*N4*-Dimethyl-N1-(3,3,3-trifluoro-1-methyl-2-oxopropyl-2-[1-(tert-butylaminocarbonyl-amino)-2,2-dimethyl-(1S)-propylcarboxamido]-(2S)-butanediamide (**68**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-1-[(dimethyl-amino)methyl]carboxamido-2,2-dimethylpropyl) carboxamido]butanediamide (**69**);

4-[(1*S*)-1-((1*S*)-2-(dimethylcarbamoyl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl] ethylcarbamoyl)-2,2-dimethylpropyl]carbamoylbutanoic acid (**70**);

*N*4,*N*4-dimethyl-*N*1-(3,3,4,4,4-pentafluoro-1-methyl-2-oxobutyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentyl carboxamido)propyl]carboxamidobutanediamide (**74**);

*N*1-[3-(benzylcarbamoyl)-3,3-difluoro-1-methyl-2-oxopropyl]-*N*4,*N*4-dimethyl-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamidobutanediamide (**75**);

3-{2-[2-(3,3-Dimethyl-butyrylamino)-3,3-dimethyl-butyrylamino]-3-dimethylcarbamoyl-propionylamino}-2-oxo-butyric acid benzyl amide (**76**);

*N*1-[2-(1,3-benzoxazol-2-yl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl -1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**77**);

Diphenyl *N*4,*N*4-dimethyl-*N*1-(1-aminoethylphosphinate)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butane diamide (**79**);.

*N*1-[2-(1,3-benzothiazol-2-yl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-di-methyl-1-(neopentylcarboxamido)propyl]carboxamido}butane diamide (**80**);

*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-[1,3]oxazolo[4,5-*b*]pyridin-2-yl-2-oxoethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**81**);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(6-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**82**);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(5-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**83**);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(4-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**84**);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(7-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**85**);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(methylcarbamoyl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**86**);

*N*1-(2-[2-(benzyloxy)ethyl]carbamoyl-1-methyl-2-oxoethyl)-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**88**);

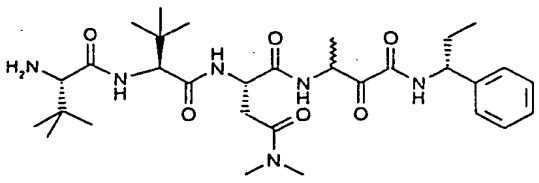
*N*1-2-[(1,3-benzodioxol-5-ylmethyl)carbamoyl]-1-methyl-2-oxoethyl-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (**89**);

*N*1-2-[(1*H*-benzo[*d*]imidazol-2-ylmethyl)carbamoyl]-1-methyl-2-oxoethyl-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**90**);

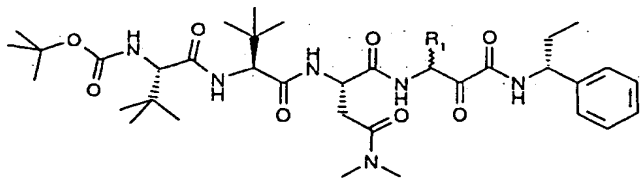
*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*S*)-1-phenylethyl]carbamoylethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**91**);

*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*R*)-1-phenylethyl]carbamoylethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**92**);

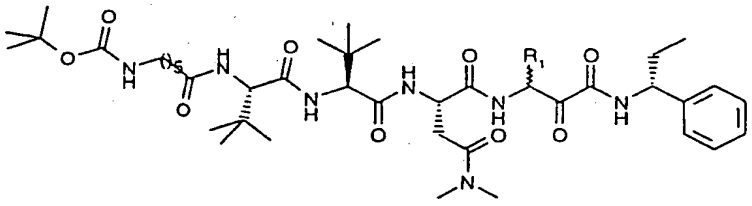
*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*R*)-1-phenylpropyl]carbamoyl-ethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**93**);



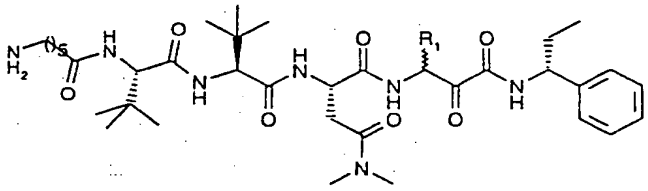
94;



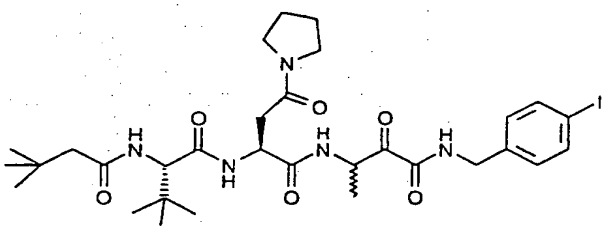
95;



96;

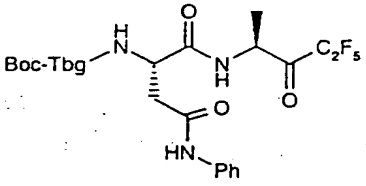


97;

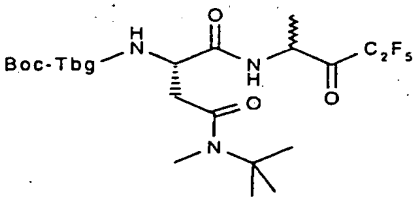


98;

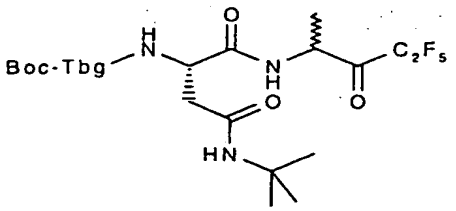
Ac-Ser-Tyr-Val-Lys-Ala(d,l)-C(O)-NH-CH_2-Ph 218;



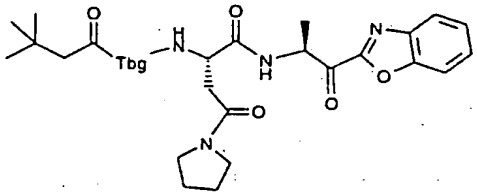
301;



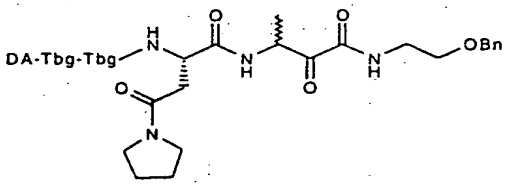
302;



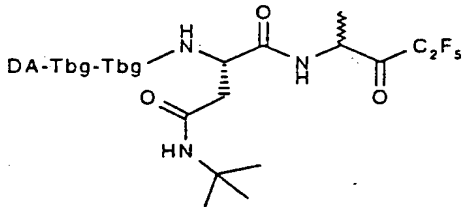
303;



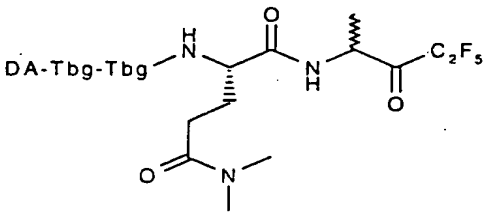
304;



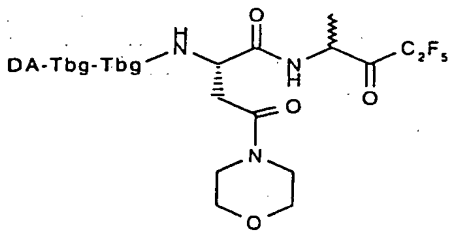
305;



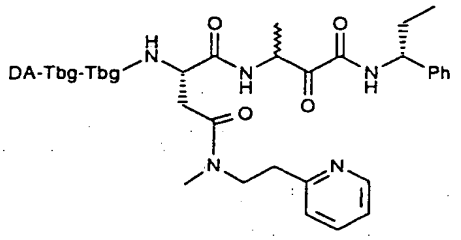
306;



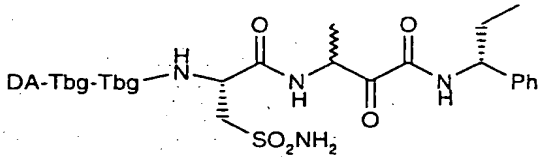
307;



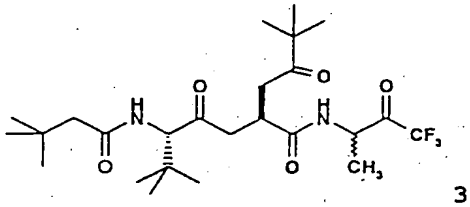
308;



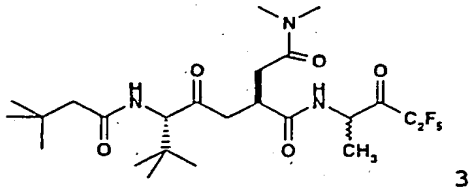
309;



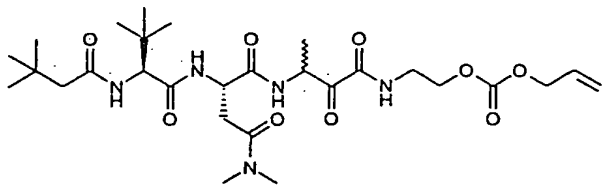
310;



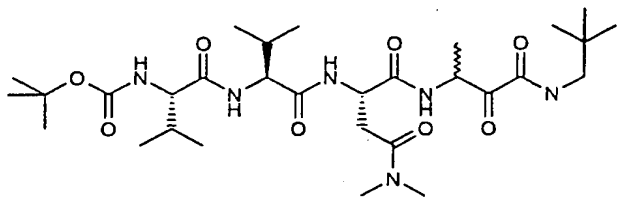
311;



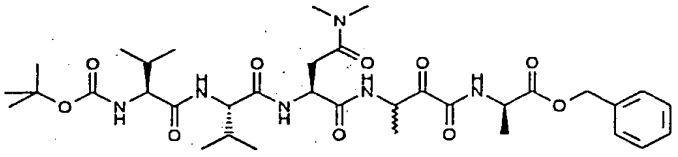
312;



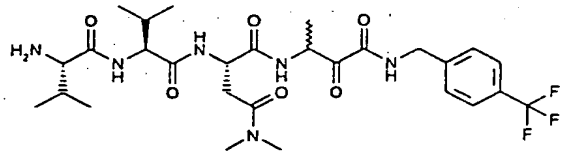
401;



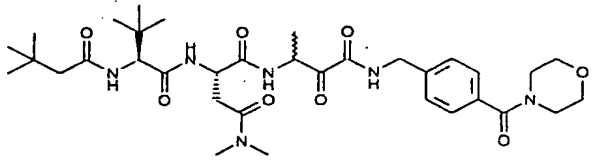
402;



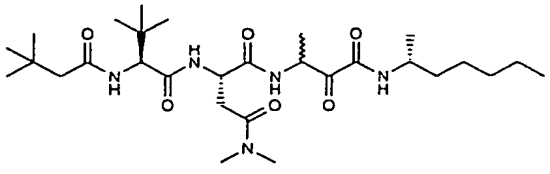
403;



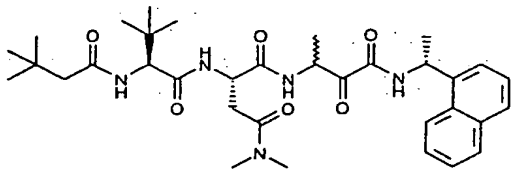
404;



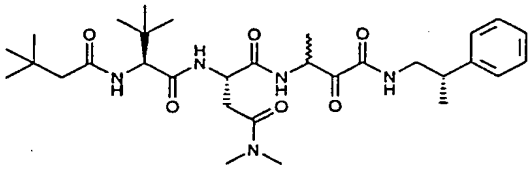
405;



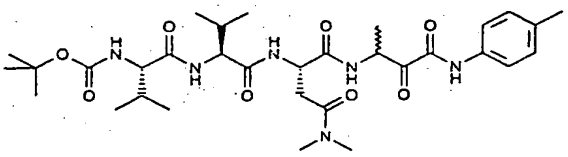
406;



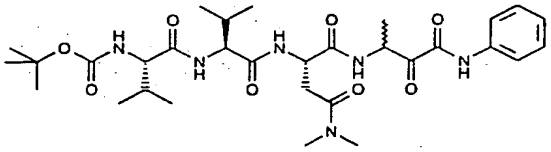
407;



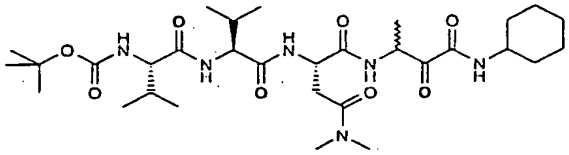
408;



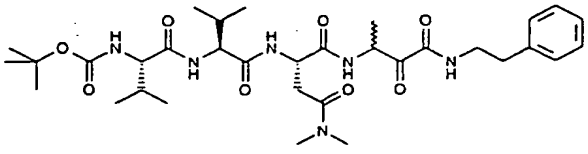
409;



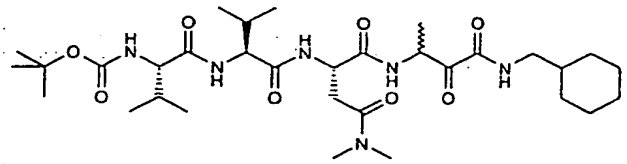
410;



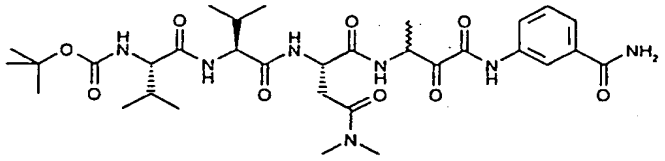
411;



412;



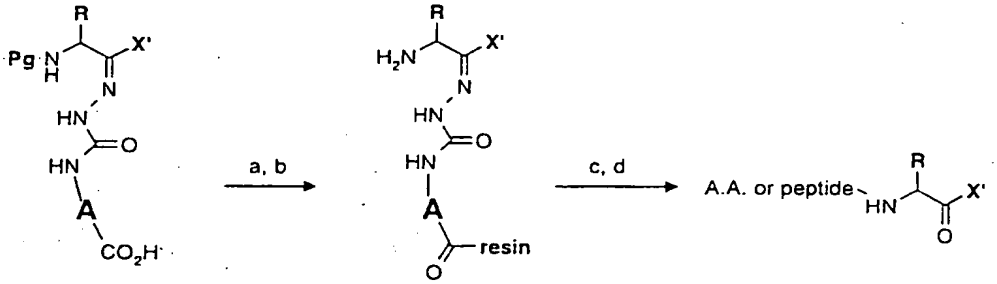
413; and



414.

A further aspect of the present invention is a solid phase process for the synthesis of peptidyl activated ketones comprising the steps of:

a) coupling a semicarbazone acid of formula **113** to a resin by *in situ* activation;



113 **103** II

wherein **R** is a side chain of a natural or non-natural amino acid;

and **X'** is CF_3, $CF_2CONH-R_{30}$, $C(O)NH-R_{30}$, or $C(O)OR_{30}$,

wherein R_{30} is a cyclic C_{3-12} alkyl or acyclic C_{1-10} alkyl or cyclic C_{3-12} alkenyl or acyclic C_{2-12} alkenyl, said alkyl or alkenyl optionally substituted with

NH_2, OH, SH, halo, or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom independently selected from the group consisting of: O, S, and N; or

R_{30} is a C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl; said aryl or aralkyl optionally containing at least one heteroatom independently selected from the group consisting of: O, S, and N;

A is a divalent spacer group which comprises a non-reactive divalent hydrocarbyl group having from 2 to 15 carbon atoms;

and

Pg is an amino protecting group

b) deprotecting said amino protecting group to give the desired resin of formula **103**;

c) coupling said resin with one or more amino acid in a sequential manner by standard chemistry; and

d) cleaving said peptide from said resin to obtain a peptidyl activated ketone of formula **II**.
Preferably, the cleavage step as herein described is carried out in THF, aq.HCl, and AcOH at a temperature of about 60°C for about 4 hours;
and said resin is filtered at least once..

Preferably, the resin is selected from the group consisting of: polystyrene or pegylated polystyrene

functionalized with benzydrylamine (BHA); 4-methyl benzydrylamine (MBHA); and aminomethyl (AM).

Preferably, the *in situ* activation is carried out with the addition of a coupling agent selected from the group consisting of: 2-(*1H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU); 2-(*1H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU); diisopropyl carbodiimide (DIC), and dicyclohexyl carbodiimide (DCC).

Preferably, the amino protecting group is selected from the group consisting of: *t*-butyloxycarbonyl (Boc); 9-fluorenylmethyloxy carbonyl (Fmoc); and allyloxy carbonyl (Alloc).

Preferably, **X'** is $C(O)NH_2CH_2$-phenyl or $C(O)OCH_2CH=CH_2$.

Preferably, **R** is selected from the group consisting of: CH_3; CH_2CH_3; $CH_2CH_2CH_3$; $(CH_2)_4NH_2$; $CH(CH_3)_2$; CH_2-phenyl; $(CH_2)_3$-NH-CH=N(NH_2).

Preferably, **A** is cyclohexyl, phenyl or benzyl.

Alternatively, a further aspect of the present invention is a resin of formula **103** as defined above.

Still, a further aspect of the present invention is the use of a resin of formula **103** for the solid phase synthesis of peptidyl activated ketones.

Detailed description of the invention

As used herein, the following definitions apply unless otherwise noted:

With reference to the instances where (*R*) or (*S*) is used to designate the configuration of a radical, e.g. R_4 of the compound of formula I, the designation is done in the context of the compound and not in the context of the radical alone.

The natural amino acids, with exception of glycine, contain a chiral carbon atom. Unless otherwise specifically indicated, the compounds containing natural amino acids with the L-configuration are preferred. However, applicants contemplate that when specified, some amino acids of the formula I can be of either D- or L- configuration or can be mixtures of D- and L-isomers, including 1:1 epimeric mixtures.

The non-natural amino acids include, but are not limited to, α-aminoadipic acid, α-γ-diamino butyric acid, ornithine, pipecolic acid, sarcosine, thyroxine, hydroxylysine, and hydroxyproline.

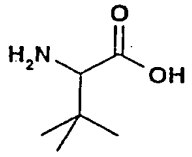
The abbreviations for some α-amino acids are set forth in **Table A**.

Table A

AMINO ACID	SYMBOL
Aminobutyric acid	Abu
Alanine	Ala
Arginine	Arg
Aspartic acid	Asp
Asparagine	Asn
Cysteine	Cys

Glutamic acid	Glu
Glutamine	Gln
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
tert-Butylglycine	Tbg
Desamino-*tert*-butylglycine	DA-Tbg
Tyrosine	Tyr
Valine	Val

As used herein the term "*tert*-butylglycine" refers to a compound of formula:



The term "side chain" with reference to an amino acid or amino acid derivative means a residue attached to the α-carbon atom of the α-amino acid. For example, the R-group side chain for glycine is hydrogen, for alanine it is methyl, for asparagine it is CH_2-C(O)NH_2, for glutamine it is $CH_2CH_2C(O)NH_2$, and *tert*-butylglycine it is *tert*-butyl. For the specific R-groups or side

chains of the α-amino acids reference is made to A.L. Lehninger's text on Biochemistry (see chapter 4).

The term "halo" as used herein means a halogen radical selected from bromo, chloro, fluoro or iodo.

The term "C_{1-10} alkyl" or "(lower)alkyl" as used herein, either alone or in combination with another radical, means cyclic or acyclic (meaning straight chain or branched) alkyl radicals containing up to ten carbon atoms and includes, for example, methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl. Obviously, as will be readily recognized by a person skilled in the art when a cycloalkyl is contemplated, unless otherwise indicated, the alkyl radical will contain at least 3 carbon atoms.

The term "C_{2-10} alkenyl" as used herein, either alone or in combination with another radical, means an alkyl radical as defined above containing from 2 to 10 carbon atoms, and further containing at least one double bond. For example alkenyl includes allyl.

The term "C_6 or C_{10} aryl" as used herein, either alone or in combination with another radical, means either an aromatic monocyclic system containing 6 carbon atoms or an aromatic bicyclic system containing 10 carbon atoms. For example, aryl includes phenyl or naphthalene.

The term "C_{7-16} aralkyl" as used herein, either alone or in combination with another radical, means an aryl as defined above linked through an alkyl group, wherein alkyl is as defined above containing from 1 to 6 carbon

atoms. Aralkyl includes for example benzyl, and butylphenyl.

The term "divalent spacer group" as used herein means a non-reactive divalent hydrocarbyl group from 2 to 15 carbon atoms and includes, but is not limited to, cyclohexane, phenyl and benzyl.

The term "heterocycle" as used herein, either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of suitable heterocycles include pyrrolidine, pyridine, thiazole, thiazolidine, benzothiazole, benzoxazole, benzimidazole, and 3,4-methylenedioxybenzene.

ANTIVIRAL ACTIVITY

The antiviral activity of the aforementioned peptidomimetic inhibitors of HCMV protease (HCMV protease inhibitors) can be demonstrated by biochemical, microbiological and biological procedures. For example, an assay based on the evaluation of the ability of the test compound to inhibit HCMV protease, an enzyme vital for viral replication.

When the HCMV protease inhibitor is employed as an antiviral agent, it is administered orally, or systemically to humans in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of

administration and standard biological practice. For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 50 to 500 mg, in a pharmaceutically acceptable carrier.

For parenteral administration, the HCMV protease inhibitor is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in standard pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the HCMV protease inhibitor will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the inhibitor compound is most desirably

administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the HCMV protease inhibitor is administered in the range of 20 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 100 mg per kilogram.

For ocular administration, the HCMV protease inhibitor is administered either topically or intraocularly (injection or implant) in a suitable preparation. For example, an implant containing the compound in a suitable formulation can be surgically placed in the posterior segment of the eye through a small incision.

With reference to systemic administration, the HCMV protease inhibitor is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. However, a dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

CHEMISTRY

The synthesis of the various inhibitors and the required intermediates are described in Schemes 2 to 7.

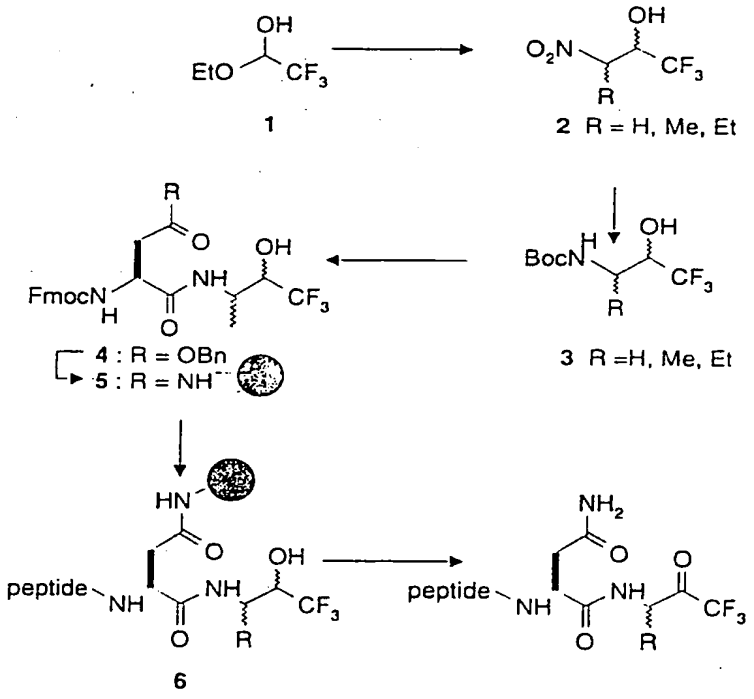
Inhibitors containing a trifluoromethyl ketone function were obtained in one of three ways: solution chemistry or solid phase synthesis: schemes 2 or 3. Inhibitors containing an α-ketoamide were obtained in one of two

ways: solid phase: scheme 3 or solution chemistry: scheme 4. Inhibitors containing other activated ketones were obtained by solution chemistry: scheme 5.

Solid phase synthesis.

Scheme 2: Inhibitors which incorporate an asparagine residue at P_2 (**Scheme 2**) could be prepared through solid phase synthesis using the asparagine side chain as an attachment point to the resin (Abraham, N. A.; Fazal, G.; Ferland, J.-M.; Rakhit, S.; Gauthier, J., A new solid phase strategy for the synthesis of mammalian glucagon, *Tetrahedron Lett.* **1991**, *32*, 577-580).

Scheme 2



Thus a Henry reaction between hemiacetal 1 and nitroethane gave nitro alcohol 2 which was immediately reduced and protected to yield alcohol 3. After removal

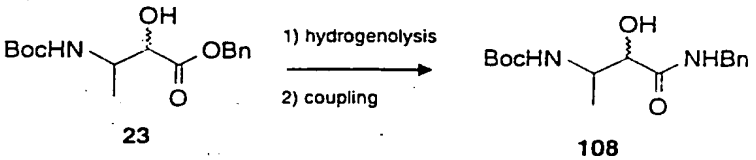
of the Boc group, coupling with a suitably protected aspartic acid derivative gave **4**. This compound was then deprotected by hydrolysis and incorporated onto a polymer support to afford the derivatized amide resin **5**. The required amino acids were then introduced by standard methods. Hydrolysis from the resin and oxidation of the resulting alcohol using Moffatt's procedure [(a) Pfitzner, K.E.; Moffatt, J.G. Sulfoxide-carbodiimide reactions. I. A facile oxidation of alcohols. *J. Am. Chem. Soc.* 1965, *87*, 5661-5670. (b) Pfitzner, K.E.; Moffatt, J.G. Sulfoxide-carbodiimide reactions. II. Scope of the oxidation reaction. *J. Am. Chem. Soc.* 1965, *87*, 5670-5678] gave the desired peptides. Activated ketones which contain a P_2 residue other than asparagine were prepared using standard solution methods from alcohol **3** or by the novel solid phase technique described below.

Schemes 3A and 3B: The synthesis of peptidyl trifluoromethyl ketone or α-ketoamide is typically performed in solution, by preparing a precursor alcohol and submitting it to a final oxidation step. This oxidation is often problematic (especially when other oxidizable groups are present in the molecule) and sometimes limits the choice of pharmacophore to be incorporated in the inhibitor.

To take advantage of the recent advances in robotics technologies and in the development of combinatorial chemistry techniques, we sought to investigate a solid phase process for the synthesis of peptidyl trifluoromethyl ketone or α-ketoamide inhibitors. Our goal was to develop a methodology which would give access directly to the activated ketone functionality

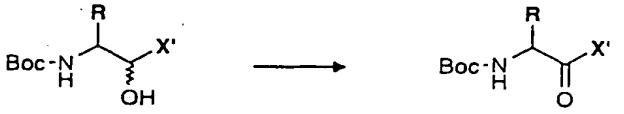
without the need to perform a final oxidation step. To this end, we considered using a semicarbazone linkage **103** (**Scheme 3A**) to serve both as reversible protecting group for the ketone and as anchoring group to the polymeric support. A similar solid phase process had already been reported by Webb and co-workers for the preparation of peptidyl aldehydes (a) Murphy, A.M.; Dagnino, R.; Pureza Jr., L.V.; Trippe, A.J.; Sherman, S.L.; Lumpkin, R.H.; Tamura, S.Y.; Webb, T.R. *J. Am. Chem. Soc.* 1992, *114*, 3156;b) Webb, T.R. United State Patent 5,283,293; c) Webb, T.R. United State Patent 5,367,072). Our process, however, comprises a final cleavage step that is performed without the requirement of formaldehyde as is described in the process of Webb et al. This allows for a greater variety of pharmacophores to be incorporated in the inhibitor.

The precursor for α-ketoamides (**108**) was prepared as follows:



23 **108**

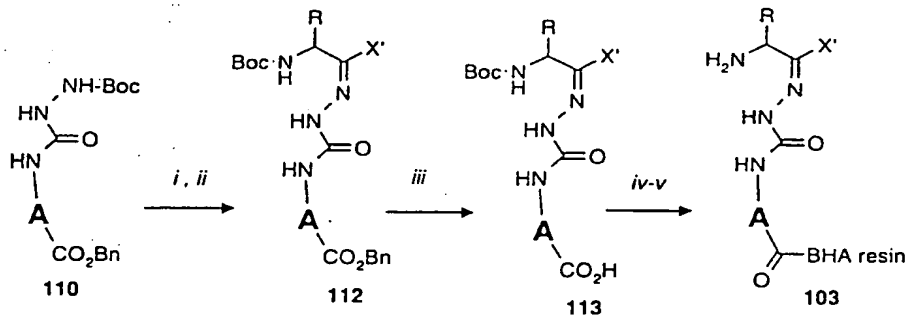
Scheme 3A



108
R: A.A. side chain
X': CF_3 or C(O)NH-Bn

109

Oxalyl chloride, DMSO / CH_2Cl_2 then Et_3N , -78 °C to 0 °C



i) 4 M HCl / Dioxane then aq. K_2CO_3 (94%) ; *ii*) 5 a-c , p-TsOH (cat.) , Toluene Reflux ; *iii*) Pd / C, H_2 (40 psi) /MeOH - EtOAc ; *iv*) BHA resin, TBTU , HOBt , DIPEA / DMSO ; *v*) 45% TFA / CH_2Cl_2 then 5% DIPEA / CH_2Cl_2

A: divalent spacer group such as cyclohexyl, phenyl or benzyl

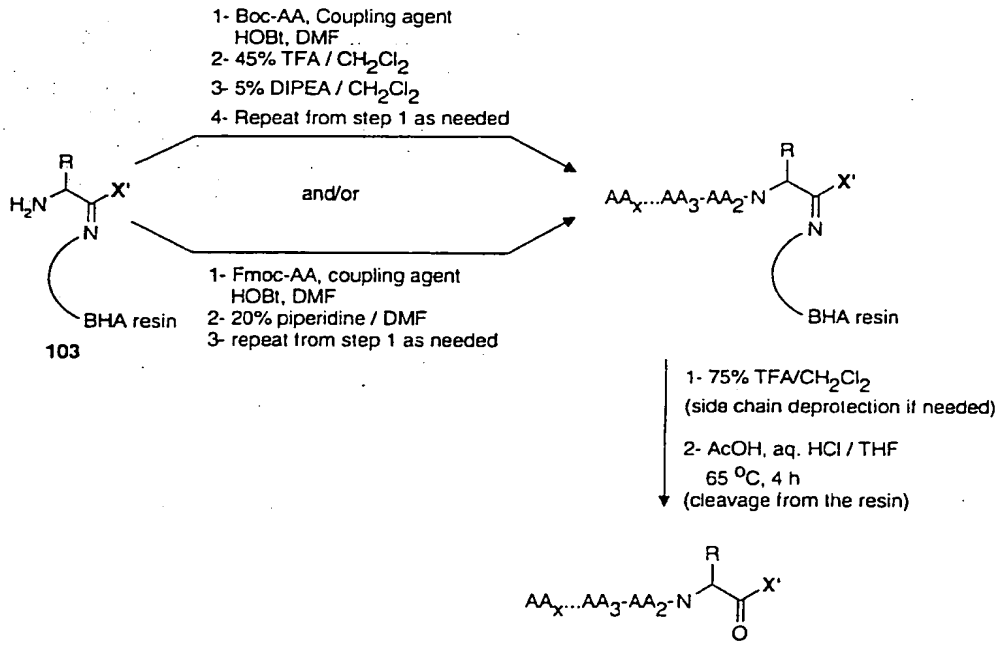
The trifluoromethyl ketone or α-ketoamide (**108**) were oxidized by a Swern oxidation to give the corresponding trifluoromethyl ketone and α-ketoamide in 66% yields.

With the necessary activated ketone in hand, it remained to generate the desired semicarbazone moiety **112** and to anchor it onto a BHA resin. To this end, the protected semicarbazide **110** was deprotected and neutralized. The resulting semicarbazide was then condensed in refluxing toluene, with the activated ketone **109** under acid catalysis and azeotropic removal of water, to give the *trans* semicarbazone **112** in moderate yield (in the case of the ketoamide, a *cis/trans* mixture was obtained). The hydrogenolysis of the benzyl ester proceeded without problem to give the corresponding acid **113** in quantitative yield. The acid was then coupled to a polystyrene BHA resin by *in situ* activation with TBTU followed by the removal of the Boc protecting group to give the desired resin **103**.

With the resin **103** in hand, the solid-phase oligomerizaton was accomplished using standard

protocols. The semicarbazone linkage being resistant to both anhydrous acidic and mildly basic conditions, both Boc and Fmoc-protected amino acids could be used at *any* position of the peptidic sequence. This versatility allowed for an increased diversity in building blocks to be incorporated in the final inhibitor. The coupling of amino acids was done through their corresponding HOBt esters as shown in **Scheme 3B**. At the completion of the synthesis, in cases where the molecule incorporated acid-sensitive side chain protecting groups, those were removed by treatment with 75% TFA / CH_2Cl_2.

Scheme 3B



The final cleavage from the polymer support was performed by refluxing the dried resin in a THF solution containing aqueous HCl and acetic acid at

65°C. In order to maximize the yields, we found it necessary to filter the resin and repeat this protocol once more. In general, the cleavage from the resin was slightly slower for the valine-derived trifluoromethyl ketones **212-217** (see Example 62) than for their alanine (**201-207**) or ethyl glycine (**208-211**) counterpart. This difference in rate of hydrolysis could be compensated for by doing one extra cleavage for valine derivatives. In cases where a basic residue was present in the sequence, a slightly higher concentration of HCl was used during the cleavage and a total of three cleavages were required in order to ensure maximum yields. We have found that addition of formaldehyde to trap the liberated semicarbazide to be superfluous. Not only the formaldehyde did not provide any significant benefit as reflected by the overall yield of compound, but it did also complicate the isolation of the desired product, particularly for sequences containing a free amino group.

During the final cleavage, no interference was observed from nucleophilic or oxidizable side chains such as the ones present in serine, methionine, tyrosine, histidine, lysine or aspartic acid. The cleavage of inhibitors containing an asparagine residues adjacent to the trifluoromethyl group was more problematic. In this case, it was found necessary to use the N-trityl protected asparagine and to deprotect the trityl group in solution after the cleavage from the resin. The presence of an asparagine residue elsewhere in the sequence did not however necessitate any side chain protection.

The cleavage conditions were mild enough to be compatible with various acid-sensitive protecting groups such as N-Boc, O-t-Bu ether, O-t-Bu ester and O-Bn ester. During the cleavage, methyl esters are however hydrolyzed to an extent of 50%. In most cases, the treatment with 75% TFA prior to the cleavage from the resin, was sufficient to completely deprotect the acid-sensitive side chain protecting groups. However, in a few examples the O-t-Bu derivative of threonine and aspartic acid were also isolated indicating that the deprotection was not complete in those cases.

α-ketoamides could also be synthesized by the same process (compounds **218** and **219** from example 62) and in similar overall yields.

By its generality, this methodology is well suited for an application in rapid lead optimization and in the generation of libraries for the purpose of identifying novel trifluoromethyl ketone and α-ketoamide inhibitors of serine proteases.

Protocols and yields of purified final products are reported in Examples 1 and 62 respectively.

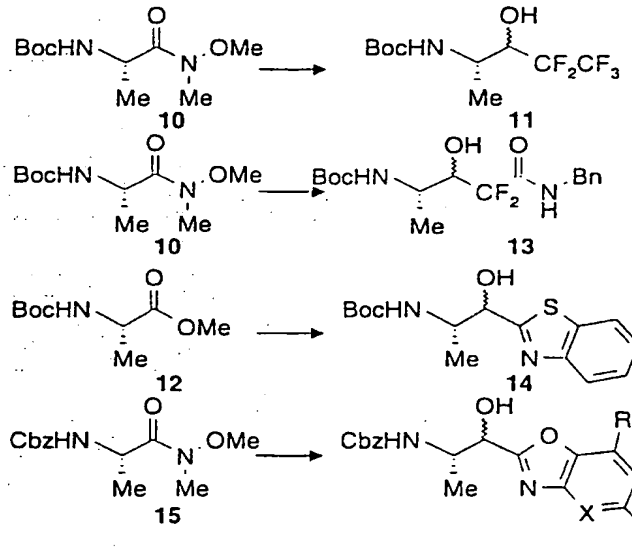
Solution chemistry.

Schemes 4, 5, and 6: Peptides containing activated ketones other than trifluoromethyl ketone could also be prepared by sequentially coupling a suitably protected amino alcohol with the required amino acids or peptide segment using standard solution methods. After the complete backbone was established, oxidation of the resulting alcohol gave the desired compound. The

preparation of the various building blocks are shown in Schemes 4, 5 and 6.

Condensation of Weinreb amide **10** with CF_3CF_2Li followed by reduction with $NaBH_4$ gave pentafluoroethyl substituted alcohol **11** (**Scheme 4**).

Scheme 4



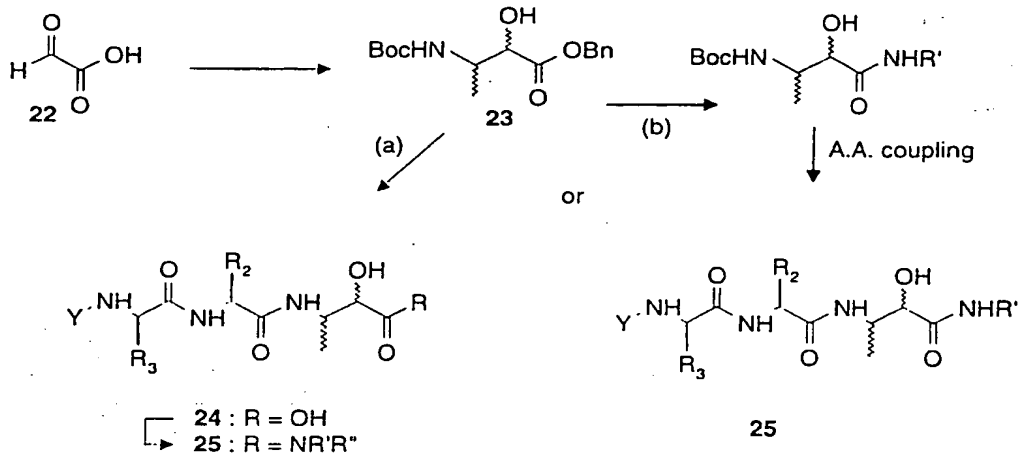
16 : X = CH, $R_1 = R_2 = R_3 = H$
17 : X = N, $R_1 = R_2 = R_3 = H$
18 : X = CCH_3, $R_1 = R_2 = R_3 = H$
19 : X = CH, $R_1 = CH_3$, $R_2 = R_3 = H$
20 : X = CH, $R_1 = R_3 = H$, $R_2 = CH_3$
21 : X = CH, $R_1 = R_2 = H$, $R_3 = CH_3$

The α,α-difluoroamide **13** was prepared from an ultrasonic Reformatsky reaction (Thaisrivongs, S.; Pals, P.T.; Kati, W.M.; Turner, S.R.; Thomasco, L.M.; Watt, W.; Design and synthesis of potent and specific renin inhibitors containing diflurostatine, difluorstatone, and related analogues. *J. Med. Chem.* 1986, *24*, 2080-2087) between ethyl bromodifluoroacetate

and Boc-alaninal followed by treatment with benzylamine. Benzothiazole **14** was obtained in a straightforward manner when 2-lithiobenzothiazole was added to this same aldehyde. The remaining benzoxazole derivatives **16** to **21** were synthesized as shown from amide **15**. Reduction to the aldehyde by the action of $LiAlH_4$ was followed by cyanohydrin formation, partial hydrolysis and cyclization using procedures previously described [(a) Edwards, P.D.; Meyer, E.F. Jr.; Vijayalakshmi, I.; Tuthill, P.A.; Andisik, D.A.; Gomes, B.; Strimpler, A. Design, synthesis, and kinetic evaluation of a unique class of elastase inhibitors, the peptidyl α-ketobenzoxazoles, and the X-ray crystal structure of the covalent complex between porcine pancreatic elastase and Ac-Ala-Pro-Val-2-benzoxazole. *J. Am. Chem. Soc.* 1992, *114*, 1854-1863. (b) Edwards, P.D.; Zottola, M.A.; Davis, M.; Williams, J.; Tuthill, P.A. Peptidyl α-ketoheterocyclic inhibitors of human neutrophil elastase. 3. *In vitro* and *in vivo* potency of a series of peptidyl α-ketobenzoxazoles. *J. Med. Chem.* 1995, *38*, 3972-3982. (c) Edwards, P.D.; Wolanin, D.J.; Andisik, D.W.; Davis, M.W. Peptidyl α-ketoheterocyclic inhibitors of human neutrophil elastase. 2. Effect of varying the heterocyclic ring on *in vitro* potency. *J. Med. Chem.* 1995, *38*, 76-85. (d) Tsutsumi, S.; Okonogi, T.; Shibahara, A.; Ohuchi, S.; Hatsushiba, E.; Patchett, A.A.; Christensen, B.G. Synthesis and structure-activity relationships of peptidyl α-keto heterocycles as novel inhibitors of prolyl endopeptidase. *J. Med. Chem.* 1994, *37*, 3492-3502].

Various α-ketoamide derivatives could also be prepared according to the alternative procedure depicted in **Scheme 5**.

Scheme 5

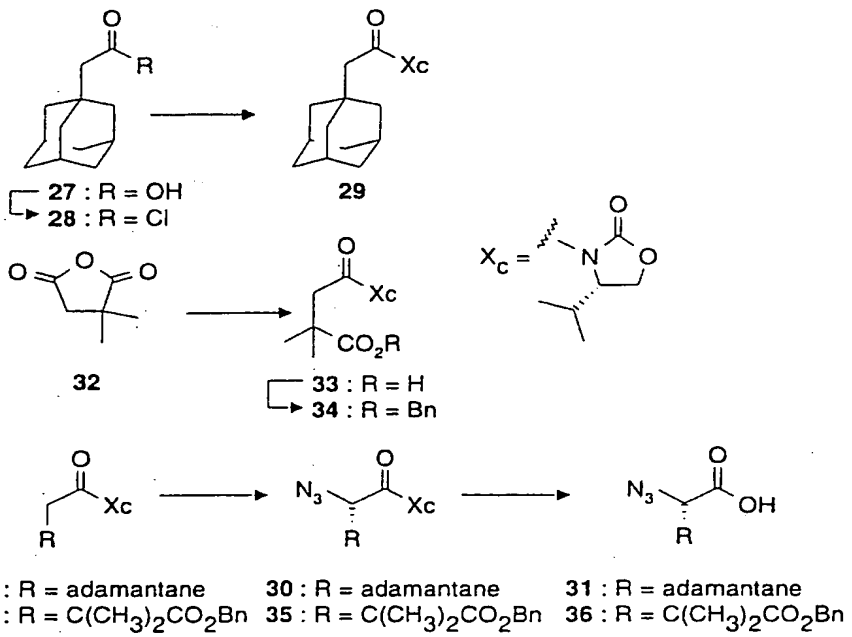


Route a: A Henry reaction between glyoxylic acid and nitroethane gave **23** after reduction and suitable protection. Coupling the required amino acids using standard methods gave **24** after removal of the benzyl ester. Incorporation of the appropriate amide function gave a series of alcohols **25** which were readily oxidized to the desired ketones using the Dess-Martin reagent (Dess, D.B.; Martin, J.C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* 1983, *48*, 4155-4156).

Route b: Alternatively, **23** could be hydrogenated to the corresponding acid and the appropriate P1' amine coupled. Coupling the required amino acids using standard methods gave **25**. The alcohol **25** was readily oxidized to the desired ketones as above.

The preparation of the unnatural amino acids adamantyl glycine and β,β-dimethyl aspartic acid are shown in **Scheme 6.**

Scheme 6



29 : R = adamantane **30** : R = adamantane **31** : R = adamantane
34 : R = $C(CH_3)_2CO_2Bn$ **35** : R = $C(CH_3)_2CO_2Bn$ **36** : R = $C(CH_3)_2CO_2Bn$

Thus oxazolidinone **29** was obtained from acid **27** using procedures described previously (Gage, J.R.; Evans, D.A. Diastereoselective aldol condensation using a chiral oxazolidinone auxiliary: (2S*, 3S*)-3-hydroxy-3-phenyl-2-methylpropanoic acid. *Org Syn.* 1989, *68*, 83-91). Formation of the enolate followed by treatment with $TrisN_3$ (Evans, D.A.; Britton, T.C.; Ellman, J.A.; Dorow, R.L. The asymmetric synthesis of α-amino acids. Electrophilic azidation of chiral imide enolates, a practical approach to the synthesis of (R)- and (S)-azido carboxylic acids. *J. Am. Chem. Soc.* 1990, *112*, 4011-4030) gave azide **30** which was hydrolyzed to yield acid **31** in a straightforward manner. To the carboxylate

group of this azido acid was then introduced the appropriate amino acid residues. Capping the N-terminus was accomplished using standard coupling methods after reduction of the azide moiety. Using a similar approach, anhydride **32** was converted to protected azido acid **36**.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying the invention, are intended to illustrate and not to limit the invention.

Examples

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. The purity of each inhibitor was determined by HPLC, ^{1}H-NMR, and/or elemental analysis. ^{1}H-NMR spectra were obtained at 400 MHz on a Bruker AMX 400 spectrometer. FAB mass spectra were recorded on an Autospec, VG spectrometer. Column chromatography was performed either on silica gel (10-40 µm or 230-400 mesh ASTM, E. Merck) or by preparative HPLC using a Partisil 10 ODS-3, C18 preparative column (50 cm x 22 mm). Analytical HPLC were carried out on the following systems; System A: Vydac C18, 10 µm analytical column (24 cm x 4.6 mm); mobile phase, acetonitrile/0.06% trifluoroacetic acid (TFA) in water/0.06% TFA; System B: Vydac C18, 5 µm analytical column (15 cm x 4.6 mm); mobile phase, acetonitrile in 50 mM NaH_2PO_4 at pH 4.4; System C: Vydac C8, 10 µm analytical column (24 cm x 4.6 mm); mobile phase, acetonitrile in 20 mM Na_2HPO_4 at pH 8.0; System D: symmetry shield C8, 10 µm analytical

column (15 cm x 3.9 mm); mobile phase, acetonitrile in 20 mM Na_2HPO_4 at pH 9.0; System E: Supelcosil C8, 5 µm analytical column (15 cm x 4.6 mm); mobile phase, acetonitrile/0.1% TFA in water/0.1% TFA at pH 2.0.

Abbreviations or symbols used in the examples, or throughout the present specification, include Boc, *tertiary* butyloxycarbonyl; BOP: benzothiazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; DA-Tbg, desamino-*tertiary*-butylglycine (3,3-dimethylbutylbutanoic acid); DCC: N,N'-dicyclohexylcarbodimide; DIC, 2-dimethylaminoisopropyl chloride hydrochloride; DMF, N,N,-dimethylformamide; DMSO, dimethylsulfoxide; DTT, dithiothreitol; EDC: 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide·hydrochloride salt; Fmoc, 9-fluorenylmethyloxycarbonyl; HCMV, human cytomegalovirus; HOBt, 1-hydroxybenzotriazole hydrate; MES, 4-morpholineethanesulfonic acid; NMP, N-methylpyrrolidone; PCR, polymerase chain reaction; Ph, phenyl; PMSF, phenylmethylsulfonyl fluoride; QSAR, quantitative structure activity relationship; Tbg, *tertiary*- butylglycine; tBu, *tertiary*-butyl; TFA, trifluoroacetic acid; Trt, triphenylmethyl; TBTU, O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TCEP, tris(2-carboxyethyl)phosphine hydrochloride; TRIS, tris(hydroxymethyl)aminomethane.

Example 1.

General procedure for the solid phase synthesis of peptides:

1- Boc/DIC/HOBt protocol.

The peptides were assembled on a ACT396 peptide synthesizer sold by Advanced Chemtech (Louisville, KT). Each reaction vessels were charged with the appropriate resins **103** (0.25 mmol) and were successively washed with 3.5 mL portions of CH_2Cl_2 (2 X), MeOH (2 X) and CH_2Cl_2 (2 X). The amino acids were coupled as their activated HOBt esters, utilizing 4.8 equivalents of the reagents as follows: A 0.5 M solution of a mixture of Fmoc-protected amino acid and HOBt in DMF (2.4 mL, 1.2 mmol of each) was added to the deprotected resin, followed by addition of a 0.5 M DIC solution in CH_2Cl_2 (2.4 mL, 1.2 mmol). The reaction vessel was shaken for 3.5 h. The reaction vessel was drained and the remaining resin was washed twice with 5 mL of CH_2Cl_2. Fresh portions of reagent solutions were added and the coupling step was repeated for 3.5 h. After the coupling, the resin was washed successively with 5 mL portions of CH_2Cl_2 (2 X), MeOH (2 X) and CH_2Cl_2 (2 X). The Boc amino protecting groups was removed with a solution of 45% TFA in CH_2Cl_2 (4 mL for 25 min) and washed as above. After the last coupling, an additional washing step with 5 mL of CH_2Cl_2 (3 X) was done and the resin was dried *in vacuo*.

2- Fmoc/TBTU/HOBt protocol.

The peptides were assembled as above except for the coupling which was done as follow: The resin was suspended in NMP (0.35 mL) and was treated with a 0.5 M solution of a mixture of Fmoc-protected amino acid and HOBt in NMP (1.8 mL, 0.9 mmol of each), a 0.5 M solution of TBTU in DMF (1.8 mL, 0.9 mmol) and a 1.0 M solution of DIPEA in NMP (1.8 mL, 1.8 mmol). The reaction vessel was shaken for 1.25 h, it was drained and the remaining resin was washed twice with 3.5 mL of DMF. Fresh portions of reagent solutions were added and the coupling step was repeated for 1.25 h. The deprotection of the Fmoc group was done by treating the resin with a 25% solution of piperidine in DMF for 25 minutes.

3- Boc/TBTU/HOBt protocol.

The peptides were assembled on a COUPLER™ 250 C (VEGA Biotechnologies) or on an ACT 90 (Advanced ChemTech) peptide synthesizer. The reaction vessel was charged with the appropriate resins **103** (0.25 mmol) which was successively washed with 15 mL portions of CH_2Cl_2 (2 X), MeOH (2 X) and CH_2Cl_2 (2 X). The amino acids were coupled as their activated HOBt esters, utilizing 3 equivalents of the reagents as follows: The resin was suspended in DMF (15 mL) and was treated with the Boc-protected amino acid (0.75 mmol), HOBt hydrate (0.75 mmol), DIPEA (1.5 mmol, 0.26 mL) and TBTU (0.75 mmol, 241 mg). The reaction vessel was shaken for 1 h and the completion of the coupling monitored by Kaiser test. In the case of incomplete couplings, the reaction vessel was drained and the resin was washed

twice with 15 mL of CH_2CL_2. Fresh reagents were added and the coupling step was repeated for an extra hour. The reaction vessel was drained and the resin washed as above. The Boc protecting group was removed by successive treatment (5 min. then 20 min.) with 15 mL of a 45% solution of TFA in CH_2Cl_2. The resin was washed with CH_2CL_2 (2 X), 5% DIPEA in CH_2CL_2 (1 min. then 5 min.), CH_2Cl_2 (2 X), MeOH (2 X) and CH_2Cl_2 (2 X).

General procedure for the cleavage of the peptidyl activated ketone from the solid support (according to scheme 3B).

The dried resin (~800 mg) was suspended in THF (9 mL), H_2O (0.50 mL), AcOH (0.25 mL) and 1M aq. HCl (0.10 mL) and was heated in a bomb at 65 ^{o}C for four hours. The solution was cooled down, filtered and treated as above one more time. In the case where the sequence contained a basic residue such as lysine or histidine, an extra 0.05 mL of 1 M HCl was used and the procedure was repeated a third time. All the mother liquors were combined, the THF was concentrated *in vacuo* and the residue was purified on reversed phase HPLC (Whatman HPLC column, 22.0 mm x 500 mm, Partisil 10 ODS-3 M/20-50, particle size 10 µm, solvents: A = 0.06 % TFA/H_2O, B = 75% CH_3CN-25% H_2O containing 0.06% TFA; gradient 0 to ~50% B in 60 min). The desired peptidyl activated ketones **201-219** were isolated in yields reported in Example 62.

Example 2.

Alternative synthesis of α-ketoamides (according to scheme 5).

Preparation of 3-{2-[2-(3,3-dimethyl-butyrylamino)-3,3-dimethyl-butyrylamino]-3-dimethylcarbamoyl-propionylamino}-2-oxo-butyric acid benzyl amide (76, Table 6).

Preparation of α-hydroxy ester 23. To a solution of nitroethane (4.0 g, 53 mmol) in ethanol (15 mL) was added aqueous NaOH (68 mL of 2N solution, 136 mmol). To this rapidly stirred solution was added glyoxylic acid (5.9 g, 64 mmol). The solution was stirred 15 h and then acidified with 10% aqueous HCl (pH 2) and the aqueous phase saturated with NaCl before extraction with EtOAc (3 x 150 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to give 8.1 g of a viscous yellow oil. This crude material was dissolved in ethanol (50 mL) containing Et_3N (18 mL, 119 mmol) and treated with di-*tert*-butyl dicarbonate (12.2 g, 56 mmol) and Raney nickel (3 g) which had been washed with water immediately before use. Hydrogenation at 45 p.s.i for 20 h afforded after filtration through Celite and concentration, the crude acid (11.1 g). A portion of the crude acid (3.07 g, 14 mmol) was dissolved in DMF (30 mL) and treated with anhydrous K_2CO_3 (4.3 g, 30.8 mmol) and benzyl bromide (2.5 mL, 21 mmol). After stirring for 3 h at room temperature, the DMF was removed under reduced pressure and the residue dissolved in EtOAc (150 mL) and washed with water (100 mL) and brine (80 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude yellow oil (4.3 g) was purified by flash chromatography on silica gel (230-400 mesh), eluting with 33% EtOAc in hexane to

provide pure benzyl ester **23** (1.8 g, 42 % from nitroethane). HPLC (system C) 99%, (system D) 97%; IR (KBr) υ 3422, 3361, 1740, 1684 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.27 (d, *J* = 12.1 Hz, 1H), 5.19 (d, *J* = 12.1 Hz, 1H), 4.82 (m, 1H), 4.36 and 4.35 (2 x d, *J* = 5.7 and 5.4 Hz, 1H), 4.11 (m, 1H), 3.10 (m, 1H), 1.43 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H); FAB MS m/z: 310 (MH^+), 210 (M - 100); HRMS calcd for $C_{16}H_{24}NO_5$ (MH^+) 310.1654, found: 310.1644; Anal ($C_{16}H_{23}NO_5$) C, H, N.

Synthesis of α-keto acid 24. The *tert*-butyloxycarbonyl (Boc) group from ester **23** (4.0 g, 12.9 mmol) was removed using 4 N HCl / dioxane (30 mL) for 45 min at 0 °C. The hydrochloride salt was obtained by concentration and coevaporation with toluene (15 mL). The HCl salt (12.9 mmol) was combined with EDC (2.6 g, 13.6 mmol, 1.1 equiv.), HOBt (1.8 g, 13.6 mmol, 1.1 equiv.) and Boc-Asn(NMe_2)-OH (3.4 g, 12.9 mmol, 1.1 equiv.) in DMF (50 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C (ice bath) before iPr_2NEt (7.9 mL, 45.3 mmol, 3.5 equiv.) was added. The solution was then stirred at room temperature for 16 h. The reaction mixture was partitioned between EtOAc (250 mL) and sat. aqueous $NaHCO_3$ (150 mL). The organic phase was washed with 5% aq. HCl (150 mL) and finally brine (150 mL). Drying ($MgSO_4$) was followed by filtration and concentration to give 6.0 g of crude material. In most cases the crude material was suitable for subsequeht couplings without purification. After the final coupling, the α-hydroxy benzyl ester peptides were purified by flash chromatography. The acid **24** was then obtained from the benzyl ester (1.10 g, 2.0 mmol) by hydrogenation over 10% Pd/C (55 mg) in ethanol (30 mL)

at atmospheric pressure over the course of a few hours to afford after filtration through a pad of Celite a white solid (0.95 g, 100% yield). HPLC (system A) 100%, (system C) 100%; IR (KBr) υ 3316, 1727, 1642 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$), mixture of 4 diastereomers, δ 8.06 and 8.01 (2 x d, J = 7.3 and 8.6 Hz, 1H), 7.87, 7.79, 7.70 and 7.54 (4 x d, J = 8.6, 8.6, 8.9 and 8.6 Hz, 1H), 7.09 and 7.03 (2 x d, J = 7.9 and 8.6 Hz, 0.5H), 6.72 (m, 0.5H), 6.52 (m, 0.25), 6.34 and 6.29 (2 x d, J = 7.6 and 7.3 Hz, 0.75H), 6.10-5.4 (br s, 1H), 4.99-4.88 (m, 0.5H), 4.87-4.78 (m, 0.5H), 4.66-4.37 (m, 2H), 4.33-4.09 (m, 1H), 3.30-3.15 (m, 0.3H), 3.05-2.85 (m, 6.7 H), 2.75-2.65 and 2.60-2.50 (m, 1H), 2.25-2.10 (m, 2H), 1.28-1.19 (m, 3H), 1.10-0.97 (m, 18H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 174.9, 173.5, 173.1, 173.0, 171.5, 171.0, 170.9, 170.8, 170.7, 170.5, 170.2, 73.03, 72.74, 60.9, 60.67, 50.3, 50.1, 49.5, 49.4, 48.1, 47.9, 47.7, 37.56, 35.9, 35.8, 35.7, 34.7, 34.4, 34.3, 33.8, 31.1, 29.9, 29.8, 26.9, 26.8, 26.7, 17.4, 17.2; FAB MS m/z: 473 (MH^+), 495 (M + 23); HRMS calcd for $C_{22}H_{41}N_4O_7$ (MH^+) 473.2975, found: 473.2990; Anal ($C_{22}H_{40}N_4O_7$) C, H, N.

Coupling of the P_1' residue was accomplished using the above general coupling protocol with the appropriate terminal amine (1.2 equiv.). The final oxidation step was performed by treatment of the prerequisite α-hydroxy amide (62 mg, 0.11 mmol) with 2 equivalents of the Dess-Martin periodinane (94 mg, 0.22 mmol) in DMF (1 mL) for 4 h. Addition of 10% sodium thiosulfate (5 mL) and sat. $NaHCO_3$ (5 mL) with stirring (15 min) was followed by extraction with EtOAc (3 x 10 mL) to give the desired α-ketoamide. Final purification was performed using preparative HPLC to afford **76** after

lyophilization, (51 mg, 82% yield) as a white solid. HPLC (system C) 100%, (system D) 96.1%; IR (KBr) υ 3316, 1641, 1529 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of diastereoisomers at P_1, δ 9.21-9.15 (m, 1H), 8.14 and 8.09 (2 x d, 7.3 and 7.6 Hz, 1H), 8.03 and 7.97 (2 x d, *J* = 6.4 and 5.7 Hz, 1H), 7.60 (d, *J* = 8.3, 1H), 7.35-7.17 (m, 5H), 5.02-4.88 (m, 1H), 4.64-4.49 (m, 1H), 4.39-4.23 (m, 2H), 4.13 and 4.12 (2 x d, *J* = 8.6 and 8.6 Hz, 1H), 2.92 and 2.91 (2 x s, 3H), 2.79 and 2.78 (2 x s, 3H), 2.74-2.54 (m, 2H), 2.19 (br d, *J* = 12.4 Hz, 1H), 2.03 and 2.02 (2 x d, *J* = 12.4 and 12.7 Hz, 1H), 1.25 and 1.23 (2 x d, *J* = 7.3 and 7.0 Hz, 3H), 0.94 and 0.91 (2 x s, 18H); FAB MS m/z: 560 (MH^+), 582 (M + 23); HRMS calcd for $C_{29}H_{46}N_5O_6$ (MH^+) 560.3448, found: 560.3426.

Example 3.

Alternative preparation of Fmoc-Asp(Rink Resin)-aminotrifluoromethyl alcohol (5) (according to scheme 2; R:Me).

4-(*tert*-butoxycarbonylamino)-1,1,1-trifluorobutan-2-ol (3). This compound was prepared according to a literature procedure analogous to the preparation of the valine analogue (Skiles, J.W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K.G.; Mauldin, S.C.; Vitous, J.; Mui, P.W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S.T.; Possanza, G.; Keirns, J.; Letts, G.; Rosenthal, A. Inhibition of human leukocyte elastase (HLE) by N-substituted peptidyl trifluoromethyl ketones. *J. Med. Chem.* 1992, *35*, 641-662). IR (KBr) υ 3313 (br), 1681, 1527 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of diastereomers, δ 6.84 and 6.43 (d, *J* =

8.4 Hz and 8.9 Hz, 1H), 6.32 and 6.24 (d, J = 6.9 and 7.4 Hz, 1H), 3.93-3.81 (m, 1.5H), 3.70 (quint, J = 7.3 Hz, 0.5H), 1.373 and 1.371 (s, 9H), 1.10 and 1.07 (d, J= 7.4 and 6.4 Hz, 3H); FAB MS m/z: 244 (MH^+); Anal ($C_9H_{16}F_3NO_3$) C, H, N.

Fmoc-Asp(Ot-Bu)-aminotrifluoromethyl alcohol (4). This compound was prepared in solution by coupling Fmoc-Asp(Ot-Bu)-OH and the alanine-derived aminotrifluoromethyl alcohol. HPLC (system A) 98%, (system B) 99%; IR (KBr) υ 3300, 1721, 1697, 1661, 1540 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 7.99-7.93 (m, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7,70 (m, 2H), 7.55 (dd, $J1$ = 15.9 Hz, $J2$ = 8.6 Hz, 1H), 7.45-7.39 (m, 2H), 7.35-7.29 (m, 2H), 6.41 (d, J = 7.0 Hz, 1H), 4.40-4.19 (m, 4H), 4.06-3.88 (m, 2H), 2.66-2.58 (m, 1H), 2.44-2.40 (m, 1H), 1.37 (s, 9H), 1.08 (d, J = 6.7 Hz, 3H); FAB MS m/z: 537 (MH^+); HRMS calcd for $C_{27}H_{32}F_3N_2O_6$ (MH^+) 537.2212, found: 537.2229.
The compound above was deprotected with 40% TFA in CH_2Cl_2 and coupled on a Rink resin with DCC/HOBt to afford **(5)**.

Example 4.
Preparation of other activated ketones (according to scheme 4).

4-(tert-butoxycarbonylamino)-1,1,1,2,2-pentafluoropentan-3-ol (11). To a dry 500 mL round bottom flask was added anhydrous Et_2O (100 mL) and a 1.5 M solution of MeLi·LiBr in Et_2O (100 mL, 150 mmol). This solution was subsequently cooled to -78 °C. A second flask was cooled to -78 °C and charged with Et_2O (100

mL) and CF_3CF_2I (44.7 g, 182 mmol). The contents of this flask were then added via canula over 15 min to the MeLi·LiBr slurry. The resulting solution was stirred for 30 min at -78 °C before the Weinreb amide **10** (10.6, 45.5 mmol) was added in one portion. The reaction was stirred at -78 °C for 90 min and then allowed to warm to -30 °C for 2 h. The reaction was quenched by the addition of sat. NH_4Cl (125 mL). The organic phase was washed with H_2O (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated to provide an orange oil. The oil was redissolved in 20 % MeOH/THF (100 mL) and transferred to a 500 mL round bottom flask. The solution was cooled to 0 °C before $NaBH_4$ (1.9g, 50.1 mmole) was added portionwise over 5 min (Caution! foaming occurs). The reaction was subsequently stirred for 1 h at 0 °C. Et_2O (200 mL) was added followed by 10% citric acid (100 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ (1 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20 % ethyl acetate in hexanes) to provide a colorless oil **11**, 12.3 g (92%). HPLC (system D) 100%, IR (KBr) υ 3368, 2987, 1687 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 25:1 mixture of diastereomers, δ 6.87 (d, J = 8.0, 1.5H), 6.42 (d, J = 8.9 Hz, 0.5H), 6.32 and 6.25 (2 x d, J = 8.0 and 8.3 Hz, 1H), 4.08-3.78 (m, 2H), 1.37 (s, 9H), 1.13 and 1.08 (2 x d, J = 7.0 and 6.7 Hz, 3H); FAB MS m/z: 294 (MH^+); HRMS calcd for $C_{10}H_{17}F_5NO_3$ (MH^+) 294.1129, found: 294.1138.

Benzyl 4-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-hydroxy-(4S)-pentanoate (13). This material was prepared using a modification of the procedure

previously described (Thaisrivongs, S.; Pals, P.T.; Kati, W.M.; Turner, S.R.; Thomasco, L.M.; Watt, W.; Design and synthesis of potent and specific renin inhibitors containing diflurostatine, difluorstatone, and related analogues. *J. Med. Chem.* 1986, *24*, 2080-2087). Thus amide **10** (14.9 g, 64.3 mmol) was dissolved in THF (230 mL) at 0 °C. $LiAlH_4$ (4.90 g, 129 mmol) was added in several portions over a period of 20 min, and the suspension was then stirred for 2 h at 0 °C. This suspension was transferred via cannula into 500 mL of 10% aqueous citric acid and stirred for 1 h. The mixture was extracted with Et_2O (3x) and the combined organic phases washed with water, brine, dried ($MgSO_4$), filtered and concentrated to give the corresponding aldehyde as a white solid (10.7 g, 97%). ^{1}H-NMR ($CDCl_3$) δ 9.57 (s, 1H), 5.09 (br, 1H), 4.23 (br, 1H), 1.46 (s, 9H), 1.34 (d, J = 7.3 Hz, 3H). Zinc dust (16.2 g, 24.8 mmol) was placed in THF (40 mL) and sonicated 30 min. A solution of the aldehyde (10.7 g, 62 mmol) and ethyl bromodifluoroacetate (20 g, 99 mmol) was added over 30 min using a syringe pump while sonicating. Sonication was continued for 1.5 h before the suspension was poured into 500 mL of 10% aqueous citric acid and extracted with EtOAc (3x). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The oil obtained contained 20% of the starting aldehyde but was used without further purification. The hydroxy ester (2.20 g, 7.40 mmol), benzylamine (3.96 g, 37.0 mmol) and *i*-Pr_2NEt (4.76 g, 37.0 mmol) were heated in refluxing ethanol for 18 h. The solution was concentrated to dryness, taken up into EtOAc and washed with 1 N HCl, brine, dried ($MgSO_4$), filtered and concentrated *in*

vacuo to give a yellow oil. This material was purified by flash chromatography using TLC grade silica gel to give **13** as a white solid (1.17g, 44% over 2 steps). HPLC (system B) 100%, (system C) 99%; IR (KBr) υ 3344, 2979, 1684 cm^{-1}; ^1H-NMR ($CDCl_3$) 4:1 mixture of isomers δ 7.20 (m, 5H), 6.90 (br s, 1H), 4.75 (m, 1H), 4.45 (m, 2H), 4.08 (br s, 1H), 3.88 (m, 2H), 1.32 (s, 9H), 1.16 (d, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6) δ 164.58, 164.30, 164.02, 155.61, 139.31, 129.11, 127.97, 127.72, 119.99, 117.47, 114.88, 78.59, 71.91, 71.65, 71.44, 46.28, 43.04, 29.10, 19.35; FAB MS m/z: 359 (MH^+); HRMS calcd for $C_{17}H_{25}F_2N_2O_4$ (MH^+) 359.1782, found: 359.1768; Anal ($C_{17}H_{24}F_2N_2O_4$) C, H, N.

(2S)-2-(*tert*-butoxycarbonylamino)-1-benzo[d][1,3]thiazol-2-yl-1-propanol (14). This compound was prepared from methyl ester **12** using the procedure previously described (Tsutsumi, S.; Okonogi, T.; Shibahara, A.; Ohuchi, S.; Hatsushiba, E.; Patchett, A.A.; Christensen, B.G. Synthesis and structure-activity relationships of peptidyl α-keto heterocycles as novel inhibitors of prolyl endopeptidase. *J. Med. Chem.* 1994, *37*, 3492-3502). Thus a solution of **12** (28.1 g, 132 mmol) in THF (50 mL) was added dropwise to a suspension of $LiAlH_4$ (3.76 g, 396 mmol) in THF (200 mL) at 0 °C. After complete addition the mixture was stirred at room temperature for one hour. Celite (34 g) was then added followed by the careful addition of water (34 mL), 2N NaOH (34 mL) and water (100 mL) and stirring was continued for an hour. The resulting white suspension was filtered, and the filter cake was washed with EtOAc. The desired alcohol

was obtained as a colorless oil (21.07 g, 91 %). ^{1}H-NMR ($CDCl_3$) δ 4.66 (br s, 1H), 3.77 (br s, 1H), 3.68-3.61 (m, 1H), 3.53-3.47 (m, 1H), 2.65 (br s, 1H), 1.45 (s, 9H), 1.14 (d, J = 6.7 Hz, 3H). To a solution of this alcohol (3.25 g, 18.5 mmol) and Et_3N (7.75 mL, 55.6 mmol) in anhydrous CH_2Cl_2 (60 mL) and DMSO (28 mL) at 0 °C was added SO_3·py (8.85 g, 55.6 mmol) in small portions. The solution was then stirred at room temperature for 1.5 h before being poured into ice water and extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give an oil which was purified by flash chromatography to give the desired aldehyde (2.34 g, 73 %) which was used immediately. ^{1}H-NMR ($CDCl_3$) δ 9.57 (s, 1H), 5.09 (br, 1H), 4.23 (br, 1H), 1.46 (s, 9H), 1.34 (d, J = 7.3 Hz, 3H). To a solution of benzothiazole (4.43 mL, 40.5 mmol) in THF (100 mL) at -78 °C was added nBuLi (26.5 mL of a 1.4M solution in hexanes, 37.15 mmol). After stirring for 30 min, a solution of the above aldehyde (2.34 g, 13.51 mmol) in THF was added. The solution was stirred for 72 min before being quenched by the addition of saturated NH_4Cl. Extraction with EtOAc was followed by a wash with brine and drying over $MgSO_4$. Flash chromatography afforded the desired product as an orange oil. HPLC (system A) 100%, (system D, pH 7.4) 100%; IR (KBr), υ 3272, 1713 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 6:1 mixture of diastereomers at P_1, δ 8.07-8.05 (m, 1H), 7.96-7.92 (m, 1H), 7.50-7.45 (m, 1H), 7.41-7.37 (m, 1H), 6.81 and 6.44 (2 x d, J = 8.6 Hz, 1H), 6.47 (d, J = 5.4 Hz, 1H), 4.92-4.90 (m, 1H), 4.03-3.96 (m, 1H), 1.32 and 1.29 (2

x s, 9H), 1.08 and 0.98 (2 x d, J = 6.7 and 6.7 Hz, 3H); FAB MS m/z: 309 (MH^+), HRMS calcd for $C_{15}H_{21}N_2O_3S$ (MH^+) 309.1273, found: 309.1283.

(2S)-2-(benzyloxycarbonylamino)-1-benzo[d][1,3]oxazol-2-yl-1-propanol (16). This compound was prepared from **15** and 2-aminophenol using the procedure previously described ((a) Edwards, P.D.; Meyer, E.F. Jr.; Vijayalakshmi, I.; Tuthill, P.A.; Andisik, D.A.; Gomes, B.; Strimpler, A. Design, synthesis, and kinetic evaluation of a unique class of elastase inhibitors, the peptidyl α-ketobenzoxazoles, and the X-ray crystal structure of the covalent complex between porcine pancreatic elastase and Ac-Ala-Pro-Val-2-benzoxazole. *J. Am. Chem. Soc.* 1992, *114*, 1854-1863). To a solution of N-benzyloxycarbonyl-(S)-alanine (20.0 g, 89.7 mmol) in CH_2Cl_2 (200 mL) at 0 °C, was added 1-1'-carbonyldiimidazole (18.2 g, 115.7 mmol). After 30 min of stirring at 0 °C, Et_3N (16.1 mL, 115.7 mmol) was added followed by the addition of O,N-dimethylhydroxylamine hydrochloride (11.3 g, 115.7 mmol). The mixture was stirred 1 h at 0 °C and then at room temperature for 4 h. CH_2Cl_2 was added and the organic phase was washed twice with 10% aqueous HCl, saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave amide **15** (24.2 g) which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ 7.4-7.3 (m, 5H); 5.65-5.55 (m, 1H), 5.15-5.05 (m, 2H), 4.82-4.74 (m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.34 (d, J = 6.9 Hz, 3H). This compound was dissolved in THF (350 mL) at 0 °C. A 1.0 M solution of $LiAlH_4$ in THF (110 mL, 110 mmol) was added dropwise over 30 min.

Stirring was then continued at room temperature for 2 h. The mixture was then cooled to 0 °C and a solution of $KHSO_4$ (22.4 g) in water (250 mL) was added carefully. After stirring at 0 °C for one hour, the solution was extracted with ether and washed twice with 10% aqueous HCl, twice with saturated $NaHCO_3$ and once with brine. The organic phase was dried ($MgSO_4$), filtered and concentration *in vacuo* to give the desired aldehyde (19.4 g) which was immediately dissolved in CH_2Cl_2 (350 mL) and cooled to 0 °C. A solution of $NaHSO_3$ (55.9 g, 540 mmol) in water (150 mL) was introduced and the resulting mixture stirred for one hour. NaCN (25.0 g, 511 mmol) was then added and stirring was continued overnight. The suspension was diluted with EtOAc (250 mL) and hexanes (250 mL) and the layers separated. Washing with water and brine was followed by drying over $MgSO_4$ to afford the desired cyanohydrin (18.26 g, 83 %) which was dissolved in benzene (350 mL) and stored at -20 °C. To a mixture of ethanol (47.1 mL, 803 mmol) and $CHCl_3$ (50 mL) at 0 °C was added AcCl (53.5 mL, 752 mmol). After stirring at 0 °C for 30 min. a solution of the above cyanohydrin (5.87 g, 25.1 mmol) in $CHCl_3$ (50 mL) was added dropwise and stirring was continued for an additional 2 h. The mixture was then concentrated *in vacuo* and taken up in ethanol (60mL). The solution was refluxed in the presence of 2-aminophenol (3.01 g) overnight. The ethanol was removed and the residue taken up in EtOAc, washed twice with 15 % NaOH, 10 % HCl, $NaHCO_3$ and brine and dried ($MgSO_4$). Flash chromatography afforded the desired compound **16** as an orange syrup (4.81 g, 59 %) which was used without further purification. An analytical sample was obtained by recrystallization

from 30 % EtOAc in hexanes. HPLC (system A) 99%, (system D) 99%: IR (KBr) υ 1692 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of diastereomers at P_1, δ 7.75-7.68 (m, 2H), 7.42-7.19 (m, 8H), 6.22 and 6.10 (2 x d, J = 6.0 and 5.4 Hz, 1H), 5.03-4.71 (m, 3H), 4.14-4.01 (m, 1H), 1.20 and 1.11 (2 x d, J = 6.7 and 7.0 Hz, 3H); FAB MS m/z: 327 (MH^+); HRMS calcd for $C_{18}H_{19}N_2O_4$ (MH^+) 327.1345, found: 327.1355; Anal ($C_{18}H_{18}N_2O_4$) C, H, N.

(2S)-2-(benzyloxycarbonylamino)-1-(oxazolo[4,5,b]pyridin-2-yl)-1-propanol (17). This material was prepared as a 1:1 mixture of isomers in 12% yield from the above cyanohydrin (978 mg, 4.18 mmol) and 2-amino-3-hydroxypyridine (505 mg, 4.60 mmol) using the procedure described above for compound **16**. An analytical sample was obtained by recrystallization from EtOAc in hexanes (one isomer). mp: 159-161 °C; IR (KBr) υ 1719, 1699 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.53 (dd, J = 4.8, 1.2 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 8.1, 5.1 Hz, 1H), 7.39-7.08 (m, 6H), 6.33 (d, J = 6.0 Hz, 1H), 5.00-4.82 (m, 2H), 4.74 (m, 1H), 4.10-4.00 (m, 1H), 1.21 (d, J = 6.7 Hz, 3H); ^{13}C-NMR (100.6 MHz, DMSO-d_6) δ 169.34, 155.32, 154.73, 146.08, 142.32, 136.99, 128.21, 127.59, 127.37, 120.57, 119.04, 69.99, 64.99, 49.91, 16.31; FAB MS m/z: 328 (MH^+); HRMS calcd for $C_{17}H_{18}N_3O_4$ (MH^+) 328.1297, found: 328.1286; Anal ($C_{17}H_{17}N_3O_4$) C, H, N.

(2S)-2-(benzyloxycarbonylamino)-1-(4-methylbenzo[d][1,3]oxazol-2-yl)-1-propanol (18). This material was prepared as a 1:1 mixture of isomers in 35% yield from the above cyanohydrin (707 mg, 3.02

mmol) and 2-amino-*m*-cresol (409 mg, 3.32 mmol) using the procedure described above for compound **16**. An analytical sample was obtained by recrystallization from EtOAc in hexanes (1.3 : 1 mixture of isomers). mp: 98 °C; IR (KBr) υ 1701, 1690 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 7H), 7.15-7.10 (m, 1H), 5.39 and 5.29 (2 x d, *J* = 7.9 and 5.4 Hz, 1H), 5.15-4.90 (m, 3H), 4.40 and 4.23 (2 x br s, 2H), 2.58 (s, 3H), 1.34 and 1.14 (2 x d, *J* = 6.7 and 7.0 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 164.82, 164.22, 156.28, 156.12, 150.72, 150.65, 139.40, 136.27, 130.61, 130.43, 128.51, 128.40, 128.14, 128.01, 127.91, 125.20, 125.14, 125.04, 124.98, 108.20, 108.13, 71.02, 70.62, 66.96, 66.77, 50.45, 50.27, 17.35, 16.39, 12.24; FAB MS m/z: 341 (MH^+); HRMS calcd for $C_{19}H_{21}N_2O_4$ (MH^+) 341.1501, found: 341.1490; Anal ($C_{19}H_{20}N_2O_4$) C, H, N.

(2S)-2-(benzyloxycarbonylamino)-1-(5-methylbenzo[d][1,3]oxazol-2-yl)-1-propanol (19). This material was prepared as a 1:1 mixture of isomers in 53% yield from the above cyanohydrin (1.10 g, 4.70 mmol) and 2-amino-*p*-cresol (636 mg, 5.17 mmol) using the procedure described above for compound **16**. An analytical sample was obtained by recrystallization from EtOAc in hexanes (7 : 1 mixture of isomers). mp: 134-135 °C; IR (KBr) υ 1718, 1691 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47-7.09 (m, 8H), 5.47 (d, *J* = 8.6 Hz, 1H), 5.12-4.87 (m, 4H), 4.54-4.30 (m, 1H), 2.44 (s, 3H), 1.32 and 1.13 (2 x d, *J* = 6.7 and 6.7 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 165.90, 165.19, 156.09, 149.04, 140.24, 136.28, 134.38, 128.34, 128.09, 127.91, 126.32, 119.87, 119.69, 110.23, 70.84, 70.57, 66.92,

66.67, 50.48, 50.29, 21.34, 17.24, 15.32; FAB MS m/z: 341 (MH^+); HRMS calcd for $C_{19}H_{21}N_2O_4$ (MH^+) 341.1501, found: 341.1490; Anal ($C_{19}H_{20}N_2O_4$) C, H, N.

(2S)-2-(benzyloxycarbonylamino)-1-(6-methylbenzo[d][1,3]oxazol-2-yl)-1-propanol (20). This material was prepared as a 1:1 mixture of isomers in 71% yield from the above cyanohydrin (1.44 g, 6.15 mmol) and 6-amino-*m*-cresol (832 mg, 6.77 mmol) using the procedure described above for compound **16**. An analytical sample was obtained by recrystallization from EtOAc in hexanes (8 : 1 mixture of isomers). mp: 108-109 °C; IR (KBr) υ 1692 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.36-7.10 (m, 7H), 5.40 and 5.32 (d, *J* = 8.9 and 8.9 Hz, 1H), 5.14-4.85 (m, 3H), 4.42-4.28 (m, 2H), 2.47 (s, 3H), 1.33 and 1.14 (2 x d, *J* = 6.7 and 6.7 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 165.08, 156.11, 151.24, 137.95, 136.28, 135.76, 128.52, 128.16, 127.99, 127.90, 125.89, 125.79, 119.38, 119.20, 111.09, 70.99, 70.69, 66.99, 66.76, 50.55, 50.26, 21.70, 17.29, 15.38; FAB MS m/z: 341 (MH^+); HRMS calcd for $C_{19}H_{21}N_2O_4$ (MH^+) 341.1501, found: 341.1490; Anal ($C_{19}H_{20}N_2O_4$) C, H, N.

(2S)-2-(benzyloxycarbonylamino)-1-(7-methylbenzo[d][1,3]oxazol-2-yl)-1-propanol (21). This material was prepared as a 1:1 mixture of isomers in 57% yield from the above cyanohydrin (609 mg, 2.60 mmol) and 6-amino-*o*-cresol (330 mg, 2.60 mmol) using the procedure described above for compound **16**. An analytical sample (1.2 : 1 mixture of isomers) was obtained by flash chromatography (30 % EtOAc in

hexanes). oil; IR (neat) υ 1705 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.35-7.10 (m, 7H), 5.50 and 5.38 (2 x d, *J* = 8.9 and 8.3 Hz, 1H), 5.15-4.90 (m, 3H), 4.41 (s, 1H), 2.36 (s, 3H), 1.35 and 1.14 (2 x d, *J* = 6.7 and 7.0 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 165.41, 164.85, 156.29, 156.12, 150.14, 139.67, 136.28, 128.50, 128.39, 128.13, 127.97, 127.84, 126.36, 126.31, 124.59, 124.51, 121.54, 117.28, 117.12, 70.99, 70.56, 66.96, 66.71, 50.42, 50.25, 17.41, 15.26, 15.08; FAB MS m/z: 341 (MH^+); HRMS calcd for $C_{19}H_{21}N_2O_4$ (MH^+) 341.1501, found: 341.1490; Anal ($C_{19}H_{20}N_2O_4$) C, H, N.

Example 5.
Preparation of unnatural amino acids (according to scheme 6).

(4*S*)-3-[2-(1-adamantyl)acetyl]-4-isopropyl-1,3-oxazolan-2-one (29). 1-Adamantaneacetic acid (1.0 g, 5.14 mmol) was dissolved in CH_2Cl_2 (15 mL) containing 1 drop of DMF. The mixture was stirred magnetically at 5 °C under an atmosphere of nitrogen and oxalyl chloride (1.1 equiv., 0.72 g, 496 µL, 5.66 mmol) was added dropwise over 20 min. After 2 h, dichloromethane was evaporated under vacuum. The residual oil was dissolved in benzene (10 mL) and concentrated to afford compound **28** (1.09 g, 100 %) as a pale yellow oil which was used as such in the next reaction. To a solution of (4*S*)-(-)-4-isopropyl-2-oxazolidinone (0.66 g, 5.14 mmol) in anhydrous THF (10 mL) at -40 °C was added dropwise n-BuLi (3.22 mL, 1.6 M in hexanes, 5.14 mmol). After 30 min at -40 °C, the reaction mixture was cooled to -78 °C. The crude acid chloride **28** (1.09 g, 5.14 mmol)

dissolved in THF (1 mL) was added dropwise. The mixture was then stirred magnetically at 0 °C for 1 h. Ethyl acetate was added and the organic phase was washed with 20% aqueous citric acid, saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The residual solid was purified by flash chromatography on silica gel, eluting with hexane / ethyl acetate (5/1) to provide pure **29** (1.26 g, 80 %) as a white solid: mp 105-107°C; $[\alpha]_D^{22}$ +62° (*c* 1.54, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.48-4.44 (m, 1H), 4.24-4.16 (m, 2H), 2.91 (d, *J* = 14 Hz, 1H), 2.71 (d, *J* = 14 Hz, 1H), 2.38-2.33 (m, 1H), 2.00-1.94 (m, 3H), 1.75-1.61 (m, 12H), 0.92 (d, *J* = 7.5 Hz, 3H), 0.89 (d, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 171.21, 154.08, 62.84, 58.54, 46.71, 42.23, 36.73, 33.81, 28.63, 28.53, 18.04, 14.68; FAB MS m/z: 306 (MH^+); HRMS calcd for $C_{18}H_{28}NO_3$ (MH^+) 306.2069, found: 306.2058; Anal ($C_{18}H_{27}NO_3$) C, H, N.

(2*S*)-2-(1-adamantyl)-2-azidoethanoic acid (31). The oxazolidinone **29** (4.2 g, 13.7 mmol) was dissolved in THF (15 mL) and was added dropwise over 15 min to a solution of potassium bis(trimethylsilyl)amide (20.1 mL, 0.69 M in THF, 13.9 mmol) at -78 °C. After 45 min at -78 °C, 2,4,6-triisopropylbenzenesulfonyl azide (4.9 g, 15.8 mmol) in THF (10 mL) at -78 °C was added in one portion to the enolate. After 5 min, glacial acetic acid (4.6 equiv, 3.8 g, 3.61 mL, 63.2 mmol) was added and the mixture was stirred at 40 °C for 1 h. Tetrahydrofuran was evaporated under reduced pressure and the residue was dissolved in a mixture of EtOAc and water. The organic phase was washed with saturated aqueous $NaHCO_3$, followed by brine, dried ($MgSO_4$), filtered and concentrated. The residual oil was

dissolved in 75 mL of hexane/ethyl acetate (2/1). After 16 h at 25 °C, the white precipitate was removed by filtration and the filtrate was concentrated to give an oily residue which was filtered through a pad of silica, washed with hexane/ethyl acetate (8/1). This material (crude **30**, 1.3 g, 27 %) was dissolved in THF/water (70 mL, 3/1) and H_2O_2 (4 equiv, 30%, 1.69 mL, 15 mmol) was added at 0 °C followed by $LiOH \cdot H_2O$ (2.1 equiv, 0.33 g, 7.88 mmol). After 45 min, 10% aqueous $Na_2S_2O_3$ (48 mL) and solid $NaHCO_3$ (0.22 g) were added. The reaction mixture was concentrated and *ca* 50 mL of water was added. The aqueous phase was washed with chloroform (4 times), acidified at 0 °C with 15% HCl, and extracted with EtOAc (3 times). The combined EtOAc extracts were dried ($MgSO_4$), filtered and concentrated to provide compound **31** (0.79 g, 90 % from crude **30**) as a white solid: mp 110-112 °C; $[\alpha]_D^{22}$ -36° (*c* 1.60, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 1H), 2.16-2.00 (m, 3H), 1.76-1.62 (m, 12H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 174.19, 72.51, 38.68, 37.50, 36.51, 28.19; FAB MS m/z: 236 (MH^+); HRMS calcd for $C_{12}H_{18}N_3O_2$ (MH^+) 236.1399, found: 236.1389; Anal ($C_{12}H_{17}N_3O_2$) C, H, N.

Benzyl 4-[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolan-3-yl]-2,2-dimethyl-4-oxobutanoate (34). n-Butyllithium (2.4 mL, 1.6 M in hexanes, 3.9 mmol) was added dropwise to a solution of (4*S*)-(-)-4-isopropyl-2-oxazolidinone (0.5 g, 3.9 mmol) in THF (5 mL) at -40 °C under an atmosphere of nitrogen. After 30 min at -40 °C, the reaction mixture was cooled to -78 °C and 2,2-dimethylsuccinic anhydride (0.5 g, 3.9 mmol) dissolved in THF (2 mL) was added dropwise. The mixture was then stirred magnetically at 0 °C for 1 h. Ethyl acetate was

added and the organic phase was washed with 20% aqueous citric acid, brine, dried ($MgSO_4$), and concentrated to afford crude **33** as a pale yellow solid (1.0 g) which was dissolved in acetonitrile (5 mL) at 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.59 g, 583 µL, 3.9 mmol) and benzyl bromide (0.67 g, 463 µL, 3.9 mmol) were added and the reaction mixture was then stirred at 25 °C for 16 h. Acetonitrile was evaporated *in vacuo*. The residue was partitioned between EtOAc and 20% aqueous citric acid. The organic phase was washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexane / ethyl acetate (4/1) to give pure **34** (0.88 g, 61 % from **32**) as a colorless oil; $[\alpha]_D^{22}$ +56° (*c* 1.30, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 5H), 5.11 (m, 2H), 4.36-4.32 (m, 1H), 4.23-4.15 (m, 2H), 3.25 (s, 2H), 2.30-2.22 (m, 1H), 1.33 (s, 3H), 1.31 (s , 3H), 0.86 (d, *J* = 7 Hz, 3H), 0.81 (d, *J* = 7 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 176.73, 170.75, 154.03, 136.25, 128.35, 127.88, 66.24, 63.44, 58.27, 45.31, 40.24, 28.31, 25.62, 25.58, 17.84, 14.56; FAB MS m/z: 348 (MH^+); HRMS calcd for $C_{19}H_{26}NO_5$ (MH^+) 348.1811, found: 348.1822; Anal ($C_{19}H_{25}NO_5$) C, H, N.

Benzyl 3-azido-2,2-dimethylsuccinic acid (36). The oxazolidinone **34** (8.67 g, 24.9 mmol) was dissolved in THF (27 mL) and was added dropwise over 15 min to a solution of potassium bis(trimethylsilyl)amide (36.5 mL, 0.69 M in THF, 25.2 mmol) at -78 °C. After 45 min at -78 °C, 2,4,6-triisopropylbenzenesulfonyl azide (8.89 g, 28.7 mmol) in THF (15 mL) at -78 °C was added in one portion to the enolate. After 5 min, glacial

acetic acid (4.6 equiv, 6.90 g, 6.56 mL, 0.12 mol) was added and the mixture was stirred at 35-40 °C for 90 min. Tetrahydrofuran was evaporated under reduced pressure and the residue was dissolved in a mixture of EtOAc and water. The organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in 150 mL of hexane/ethyl acetate (2/1). After 16 h at 25 °C, the white precipitate was removed by filtration and the filtrate was concentrated to give an oil which was filtered through a pad of silica and rinsed with hexane/ethyl acetate (5/1). This pale yellow oil (crude **35**, 5.37 g, 55 %) was dissolved in THF/water (260 mL, 3/1) and H_2O_2 (4 equiv, 30%, 6.24 mL, 55 mmol) was added at 0 °C, followed by $LiOH \cdot H_2O$ (2.1 equiv, 1.22 g, 29 mmol). After 45 min, 10% aqueous $Na_2S_2O_3$ (175 mL) and solid $NaHCO_3$ (0.81 g) were added. Tetrahydrofuran was evaporated and the aqueous phase was extracted with chloroform (continuous liquid-liquid extraction, 24 h). The aqueous phase was then acidified with concentrated HCl at 0 °C, and extracted with EtOAc (3 times). The combined EtOAc extracts were dried ($MgSO_4$), filtered and concentrated. The residual oil was purified by flash chromatography on Merck silica gel eluting with ethyl acetate/acetic acid (400/1) to give compound **36** (0.82 g, 21 %) as a colorless oil; $[\alpha]_D^{22}$ -74° (*c* 1.43, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 -7.32 (m, 5H), 5.20-5.12 (m, 2H), 4.48 (s, 1H), 1.34 (s, 3H), 1.29 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 174.74, 173.86, 135.42, 128.56, 128.35, 128.13, 67.86, 67.18, 45.98, 23.01, 20.29; FAB MS m/z: 278 (MH^+); HRMS calcd for $C_{13}H_{16}N_3O_4$ (MH^+) 278.1141, found: 278.1130; Anal ($C_{13}H_{15}N_3O_4$) C, H, N.

Example 6.
***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-2-methyl-1-[((1*S*)-2-methyl-1-[(methylcarboxamido)methyl] carboxamidopropyl) carboxamido]propylcarboxamido) butanediamide (37, Table 1).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 97%, (system B) 98%; IR (KBr) υ 3400-3000 (br), 1637, 1548 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.51 and 8.49 (d, J = 6.0 and 6.0 Hz, 0.5H), 8.08-8.02 (m, 2H), 7.83-7.76 (m, 2H), 7.47-7.30 (m, 1.5H), 6.95-6.88 (m, 2H), 4.61-4.52 (m, 1.5H), 4.26-4.06 (m, 2.5H), 3.79-3.67 (m, 2H), 2.67-2.32 (m, 2H), 1.99-1.93 (m, 2H), 1.85 (s, 3H), 1.26 and 1.25 (d, J = 4.1 and 3.8 Hz, 1.5H), 1.06 (d, 6.7 Hz, 1.5H), 0.84-0.79 (m, 12H); FAB MS m/z: 553 (MH^+); HRMS calcd for $C_{22}H_{36}F_3N_6O_7$ (MH^+) 553.2597, found: 553.2617.

Example 7.
***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-6-amino-2-((1*S*)-1-[((1*S*)-1-[(1*S*)-2-hydroxy-1-(methylcarboxamido) ethyl]carboxamido-2-(4-hydroxyphenyl)ethyl)carboxamido]-2-methylpropyl-carboxamido)hexanamide (38, Table 1).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 98%, (system B) 99%; IR (KBr) υ 3500-2800 (br), 1643, 1516 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 3:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomer at P_1, δ 9.14 (s, 1H), 8.71 and

8.68 (d, J = 5.7 and 5.7 Hz, 0.25H), 8.08 and 8.03 (d, J = 8.0 and 8.0 Hz, 1H), 7.91 (t, J = 7.1 Hz, 2H), 7.75 (quartet, J = 7.9 Hz, 1H), 7.63 (br s, 3H), 7.57 and 7.56 (d, J = 10.9 and 8.9 Hz, 1H), 7.02-6.95 (m, 2.75H), 6.61 (d, J = 8.3 Hz, 2H), 4.94 (m, 1 H), 4.71-4.62 (m, 0.25H), 4.43 (m, 1H), 4.26 (m, 2H), 4.13 (m, 1.75H), 3.48 (t, J = 5.7 Hz, 2H), 2.92 (m, 1H), 2.74 (br m, 3H), 1.95 (q, J = 6.8 Hz, 1H), 1.83 (s, 3H), 1.62 (m, 1H), 1.51 (m, 2H), 1.08 (m, 3H), 1.08 and 1.07 (d, J = 6.7 and 6.6 Hz, 3H), 0.86-0.81 (m, 6H); FAB MS m/z 661 (MH^+); HRMS calcd for $C_{29}H_{44}F_3N_6O_8$ (MH^+) 661.3173, found: 661.3195.

Example 8.

***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamidopropyl) carboxamido]butanediamide (39, Table 1).** This compound was prepared in solution using standard coupling methods from **3** (Example 3) and oxidation of the trifluoromethyl alcohol with the Moffatt-Pfitzner method. Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system B) 100%; IR (KBr) υ 3600-2800, 1636, 1546 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 3:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.53 (m, 0.25H), 8.09 and 8.06 (d, J = 7.9 and 7.4 Hz, 1H); 7.89 and 7.87 (d, J = 4.9 and 5.4 Hz, 1H), 7.72 and 7.70 (d, J = 4.5 and 4.0 Hz, 1H), 7.46 (d, J = 9.8 Hz, 0.4H), 7.37-7.30 (m, 1.5H), 6.96-6.89 (m, 2.6H), 4,54 (m, 1H), 4.21-4.06 (m, 3H), 2.48-2.34 (m, 2H), 2.00-1.91 (m, 2H), 1.871 and 1.868 (s, 3H), 1.27 and 1.25 (d, J = 4.5 and 3.9 Hz, 0.75H), 1.06 (d, 6.9 Hz, 2.25H), 0.84-0.80 (m, 12H); FAB MS

m/z: 496 (MH^+); HRMS calcd for $C_{20}H_{33}F_3N_5O_6$ (MH^+) 496.2382, found: 496.2387.

Example 9.

***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-{[(1*S*)-2-methyl-1-[(methylcarboxamido)-propyl]carboxamido}butanediamide (40, Table 1).** This compound was prepared by solution using standard coupling methods. Final oxidation of the trifluoromethyl alcohol was accomplished with the Moffatt-Pfitzner method. HPLC (system A) 100%, (system D) 98%; IR (KBr) υ 1685, 1655, 1627 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 7:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.19 and 8.11 (2 x d, J = 7.6 and 7.6 Hz, 1H), 7.94 (m, 1H), 7.38 (m, 2H), 6.91 (m, 3H), 4.51 (m, 1H), 4.10 (m, 2H), 2.40 (m, 1H), 1.94 (m, 1H), 1.89 and 1.87 (2 x s, 3H), 1.26 (m, 0.4H), 1.07 (d, J = 5.4 Hz, 2.6H), 0.83 (t, J = 6.3 Hz, 6H); FAB MS m/z: 397 (MH^+), 415 (M + 19); HRMS calcd for $C_{15}H_{24}F_3N_4O_5$ (MH^+) 397.1699, found: 397.1712.

Example 10.

***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-(methylcarboxamido)butanediamide (41, Table 1).** This compound was prepared in solution using standard coupling methods from **3** (Example 3) and oxidation of the trifluoromethyl alcohol with the Moffatt-Pfitzner method. HPLC (system A) 99%, (system D) 99%; IR (KBr) υ 3387, 1696, 1653 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) 1 : 1 mixture of diastereoisomers at P_1, δ 8.65 and 8.59 (2 x d, J = 6.1 and 5.7 Hz, 0.1H), 8.09 and 8.04 (2 x d, J = 7.9 and 7.9 Hz, 1H), 7.53 and 7.36 (2 x d, J = 9.2 and

9.2 Hz, 1H), 7.31 (br s, 1H), 6.96-6.87 (m, 3H), 4.61-4.47 (m, 1H), 4.05-4.15 (m, 1H), 2.49 and 2.31 (m, 2H), 1.25 (dd, J = 7.0 and 4.4 Hz, 0.3H), 1.07 (dd, J = 7.0 and 3.5 Hz, 2.7H); FAB MS m/z: 298 (MH^+), 316 (M + 19); HRMS calcd for $C_{10}H_{15}F_3N_3O_4$ (MH^+) 298.1015, found: 298.1026.

Example 11.

***N*1-(3,3,3-trifluoro-(1*R*)-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2-methyl-1-(methylcarbox-amido)propyl] carboxamidobutanediamide (42, Table 1).** This compound was prepared in solution using standard coupling methods from **3** (Example 3) and oxidation of the trifluoromethyl alcohol with the Moffatt-Pfitzner method. Final purification was performed by preparative HPLC. HPLC (system A) 99%, (system D) 97%; IR (KBr) υ 1685, 1671, 1638 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), 20:1 mixture of hydrate/non-hydrate, δ 8.11 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.35 (br s, 1H), 7.32 (d, J = 9.3 Hz, 1H), 6.92 (br s, 1H), 4.52 (q, J = 7.2 Hz, 1H), 4.11 (m, 2H), 2.45 (m, 2H), 1.95 (m, 1H), 1.26 (d, J = 6.9 Hz, 0.05H), 1.07 (d, J = 6.9 Hz, 2.95H), 0.84 (t, J = 6.6 Hz, 6H); FAB MS m/z: 397.3 (MH^+), 415.3 (M + 19); HRMS calcd for $C_{15}H_{23}F_3N_4O_3$ (MH^+) 397.1699, found: 397.1707.

Example 12.

***N*1-(3,3,3-trifluoro-(1*S*)-methyl-2-oxopropyl)-(2*S*)-2-{[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamido}butanediamide (43, Table 1).** This compound was separated from **42** by preparative HPLC. HPLC (system A) 97%, (system D) 100%; IR (KBr) υ 1685, 1663, 1626

cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) hydrated form only, δ 8.19 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 9.6 Hz, 1H), 7.34 (br s, 1H), 6.90 (br s, 1H), 4.51 (q, *J* = 6.9 Hz, 1H), 4.11 (m, 2H), 2.45 (m, 2H), 1.93 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.84 (m, 6H); FAB MS m/z: 397 (MH^+), 415 (M + 19); HRMS calcd for $C_{15}H_{23}F_3N_4O_3$ (MH^+) 397.1699, found: 397.1712.

Example 13.

***N*1-(1-ethyl-3,3,3-trifluoro-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamidopropyl) carboxamido]butanediamide (44, Table 1).** This compound was prepared on solid phase using the activated ketone resin substituted as the ethyl analog (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system D) 100%; IR (KBr) υ 1640 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 7:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.55-8.47 (m, 0.14H), 8.09 and 8.05 (2 x d, *J* = 7.3 and 7.3 Hz, 1H), 7.90-7.87 (m, 1H), 7.71-7.68 (m, 1H), 7.40-7.24 (m, 2H), 6.92-6.77 (m, 3H), 4.59-4.52 (m, 1H), 4.23-4.15 (m, 2H), 3.96-3.87 (m, 1H), 2.67-2.32 (m, 2H), 2.01-1.90 (m, 2H), 1.87 and 1.86 (2 x s, 3H), 1.79-1.71 (m, 1H), 1.40-1.28 (m, 1H), 0.89-0.74 (m, 15H); FAB MS m/z: 510 (MH^+), 528 (M+19); HRMS calcd for $C_{21}H_{35}F_3N_5O_6$ (MH^+) 510.2539, found: 510.2558.

Example 14.

***N*1-(1-(3,3,3-trifluoro-1-propyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methyl-carboxamido)propyl] carboxamidopropyl)**

carboxamido]butanediamide (45, Table 1). This compound was prepared by the same procedure as for 3 (Example 3), except 1-nitroethane was replaced by 1-nitrobutane. Standard solution coupling conditions were used to prepare the peptide inhibitor with final oxidation of the trifluoromethyl alcohol using Moffatt-Pfitzner method. Purification was performed by preparative HPLC. HPLC (system A) 89%, (system D) 99%: IR (KBr) υ 3280, 1663, 1637, 1546 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), 7:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.50 (m, 0.25H), 8.18 (d, J = 7.3 Hz, 0.12H), 8.07 (m, 1H), 8.02 (d, J = 7.95 Hz, 0.25H), 7.89 and 7.88 (2 x d, J = 8.6 and 8.9 Hz, 1H), 7.77 (d, J = 8.3 Hz, 0.12H), 7.70 (d, J = 8.6 Hz, 1H), 7.46-7.24 (m, 2H), 6.97-6.72 (m, 2.7H), 4.63-4.51 (m, 1H), 4.30 and 4.28 (2 x d, J = 6.7 and 6.7 Hz, 0.12H), 4.24-4.13 (m, 2H), 4.09-3.96 (m, 1H), 2.50-2.32 (m, 2H), 2.02-1.91 (m, 2H), 1.87 (s, 3H), 1.72-1.57 (m, 1H), 1.43-1.21 (m, 2H), 1.18-1.04 (m, 1H), 0.89-0.75 (m, 15H); FAB MS m/z: 524 (MH^+), 542 (M + 19); HRMS calcd for $C_{22}H_{37}F_3N_5O_6$ (MH^+) 524.2696, found: 524.2705.

Example 15.

***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamidopropyl) carboxamido]pentanediamide (46, Table 2).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 86%, (system D) 82%; IR (KBr) υ 3281, 3079, 1647 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6), 2:3 mixture of hydrate/non-hydrate, 1.2:1 mixture of diastereoisomers at P_1, δ 8.72 (d, J = 5.7 Hz,

0.16H), 8.70 (d, J = 5.7 Hz, 0.18H), 7.90-8.02 (m, 0.8H), 7.90 (d, J = 8.9 Hz, 1H), 7.68-7.74 (m, 1H), 7.56-7.61 (m, 0.3H), 7.10-7.21 (m, 1H), 6.90-7.00 (m, 1H), 6.70-6.75 (m, 1H), 4.60-4.69 (m, 0.4H), 4.07-4.29 (m, 3.7H), 2.00-2.09 (m, 2H), 1.90-1.98 (m, 2H), 1.86 (s, 3H), 1.83-1.61 (m, 2H), 1.28 (d, J = 7.0 Hz, 0.5H), 1.27 (d, J = 7.0 Hz, 0.6H), 1.08 (d, J = 6.5 Hz, 1.4H), 1.07 (d, J = 6.4 Hz, 1.2H), 0.81-0.84 (m, 12H); FAB MS m/z: 510 (MH^+); HRMS calcd for $C_{21}H_{35}F_3N_5O_6$ (MH^+) 510.2539, found: 510.2521.

Example 16.

(3*S*)-3-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido-propyl)carboxamido]-3-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]propanoic acid (47, Table 2). This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 96%, (system B) 97%; IR (KBr) υ 3500-2800 (br), 1639, 1546 cm^{-1}; ^1H- NMR (400 MHz, DMSO-d_6), hydrated form only, 1:1 mixture of diastereomers at P_1, δ 12.29 (br s, 1H), 8.22 and 8.14 (d, J = 7.8 and 7.9 Hz, 1H), 7.89 (m, 1H), 7.70 (m, 1H), 7.40 and 7.35 (d, J = 8.8 and 9.4 Hz, 1H), 6.93 (t, J = 7.8 Hz, 2H), 4.53 (m, 1H), 4.17 (m, 2H), 4.11 (q, J = 6.9 Hz, 1H), 2.67-2.58 (m, 1H), 2.47 (m, 1H), 1.94 (m, 2H), 1.87 (s, 3H), 1.06 (m, 3H), 0.83 (m, 12H); FAB MS m/z: 497 (MH^+); HRMS calcd for $C_{20}H_{32}F_3N_4O_7$ (MH^+) 497.2223; found: 497.2237.

Example 17.

***N*1-[(1*S*)-1-((1*S*)-2-hydroxy-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)-2-**

methylpropyl]-(2*S*)-3-methyl-2-(methylcarboxamido) butanamide (48, Table 2). This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 94%, (system B) 99%; IR (KBr) υ 3500-2800, 1637, 1543 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), hydrated form only, 1:1 mixture of diastereomers at P_1, δ 7.94 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.9 Hz, 1H), 7.73 and 7.71 (d, J = 5.4 and 4.9 Hz, 1H), 7.55 and 7.50 (8.9 and 9.4 Hz, 1H), 6.93 (br m, 2H), 4.31-4.10 (m, 4H), 3.57-3.47 (m, 3H), 1.97 (m, 2H), 1.87 (s, 3H), 1.09 and 1.08 (d, J = 6.9 and 6.9 Hz, 3H), 0.86-0.81 (m, 12H); FAB MS m/z: 469 (MH^+); HRMS calcd for $C_{19}H_{32}F_3N_4O_6$ (MH^+) 469.2274, found: 469.2261.

Example 18.
***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-6-amino-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]hexanamide (49, Table 2).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 98%, (system B) 96%; IR (KBr) υ 3227, 1638, 1545, 1189 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), hydrated form only, 1:1 mixture of diastereomers at P_1, δ 7.99 (2 x d, J = 7.9 and 7.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.71 and 7.70 (2 x d, J = 8.7 and 8.4 Hz, 1H), 7.58 (t, J = 8.9 Hz, 1H), 6.99 (m, 2H), 4.29-4.09 (m, 4H), 2.73 (m, 2H), 2.00-1.92 (m, 2H), 1.93 (s, 3H), 1.63-1.46 (m, 4H), 1.28-1.25 (m, 2H), 1.09 and 1.07 (2 x d, J = 6.9 and 6.9 Hz, 3H), 0.85-0.82 (m, 12H); FAB MS (FAB) m/z: 510 (MH^+), 528 (M + 19); HRMS calcd for $C_{22}H_{39}F_3N_5O_5$ (MH^+) 510.2903, found: 510.2888.

Example 19.
***N*1-[(1*S*)-2-methyl-1-((1*S*)-2-(1,3-thiazol-4-yl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)-carbamoyl]ethylcarbamoyl) propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (50, Table 2).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 98%, (system D) 98%; IR (KBr) υ 3276, 3084, 1638 cm^{-1}; ^1H-NMR (400MHz, DMSO-d_6), 1 : 1.2 hydrate/non-hydrate, 1.2 : 1 mixture of diastereomers at P_1, δ 8.99 (d, J = 5.4 Hz, 0.55H), 8.98 (d, J = 5.4 Hz, 0.45H), 8.77 (d, J = 5.7 Hz, 0.19H), 8.71 (d, J = 5.7 Hz, 0.23H), 8.09-8.17

(m, 1H), 7.84-7.88 (m, 1H), 7.67-7.90 (m, 1.43H), 7.55 (d, J = 8.9 Hz, 0.25H), 7.29-7.34 (m, 1H), 6.94 (br s, 0.75H), 4.58-4.73 (m, 1.5H), 4.06-4.18 (m, 2.5H), 2.97-3.17 (m, 2H), 1.86-1.93 (m, 2H), 1.86 (s, 1.65H), 1.85 (s, 1.35H), 1.22 (d, J = 6.7 Hz, 0.61H), 1.21 (d, J = 6.7 Hz, 0.74H), 1.07 (d, J = 7.0 Hz, 0.93H), 0.98 (d, J = 6.7 Hz, 0.72H), 0.76-0.80 (m, 12 H); FAB MS m/z: 536 (MH^+), 554 (M + 19); HRMS calcd for $C_{22}H_{33}F_3N_5O_5S$ (MH^+) 536.2154, found: 536.2170.

Example 20.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]butanediamide (51, Table 2).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system B) 99%; IR (KBr) 1638 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of diastereomers at P_1, δ 8.56-8.49 (m, 0.1H), 8.10-8.03 (m, 0.8H), 7.89-7.86 (m, 0.8H), 7.73-7.70 (m, 0.8H), 7.44-7.41 (m, 1H), 6.95-6.80 (m, 1.5H), 4.63-4.54 (m, 1H), 4.20-4.06 (m, 3H), 2.94-2.93 (m, 3H), 2.80-2.78 (m, 3H), 2.67-2.62 (m, 2H), 1.99-1.93 (m, 2H), 1.87-1.86 (m, 3H), 1.30-1.25 (m, 0.5H), 1.07-1.06 (m, 2.5H), 0.84-0.83 (m, 12H); FAB MS m/z: 524 (MH^+); HRMS calcd for $C_{22}H_{37}F_3N_5O_6$ (MH^+) 524.2696, found: 524.2710.

Example 21.

***N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-4-methyl-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]pentanamide (52, Table 2).**

This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 97%, (system D) 97%; IR (KBr) υ 3268, 3080, 1632 cm^{-1}; ^1H-NMR (400MHz, DMSO-d_6), 1 : 1.2 hydrate/non-hydrate, 1.2 : 1 mixture of diastereomers at P_1, δ 8.72 (d, *J* = 6.5 Hz, 0.25H), 8.70 (d, *J* = 6.5 Hz, 0.3H), 7.91-8.10 (m, 1H), 7.84-7.88 (m, 1H), 7.74-7.80 (m, 1H), 7.55 (d, *J* = 8.6 Hz, 0.2H), 7.53 (d, *J* = 8.9 Hz, 0.25H), 6.90-6.96 (m, 1H), 4.57-4.68 (m, 0.5H), 4.26-4.39 (m, 1H), 4.15-4.21 (m, 1H), 4.05-4.14 (m, 1.4H), 1.87-1.95 (m, 2H), 1.85 (s, 3H), 1.53-1.63 (m, 1H), 1.30-1.50 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 0.8H), 1.25 (d, *J* = 7.0 Hz, 1H), 1.07 (d, *J* = 6.7Hz, 0.8H), 1.06 (d, *J* = 6.7 Hz, 0.6H), 0.78-0.88 (m, 18H); FAB MS m/z: 495 (MH^+); HRMS calcd for $C_{22}H_{38}F_3N_4O_5$ (MH^+) 495.2794, found: 495.2803; Anal ($C_{22}H_{37}F_3N_4O_5 \cdot H_2O$) C, H, N.

Example 22.

***N*1-[(1*S*)-2-methyl-1-((1*S*)-2-phenyl-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-ethylcarbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butan-amide (53, Table 2).**

This compound was prepared by solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 98%, (system B) 100%; IR (KBr) υ 3280, 1636, 1546 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 1 : 1 mixture of diastereomers at

P_1, δ 8.03 (m, 1H), 7.86 (m, 1H), 7.64 (m, 1H), 7.22 (m, 5H), 7.19 (m, 1H), 6.93 and 6.90 (2 x d, J = 14.3 and 13.7 Hz, 2H), 4.63-4.54 (m, 2H), 4.16-4.05 (m, 4H), 3.00-2.66 (m, 2H), 1.86 (s, 3H), 1.85 (m, 2H), 1.25, 1.21, 1.09 and 0.96 (4 x d, J = 7.4, 6.8, 6.9 and 7.9 Hz, 3H), 0.79 (m, 12H); FAB MS m/z: 529 (MH^+), 547 (M + 19); HRMS calcd for $C_{25}H_{36}F_3N_4O_5$ (MH^+) 529.2638, found: 529.2619.

Example 23.

***N*1-[(1*S*)-2-methyl-1-((1*S*)-2-methyl-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-propylcarbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (54, Table 2).**

This compound was prepared on solid phase using the activated ketone resin (Example 1). HPLC (system A) 84%, (system B) 83%; IR (KBr) 1633 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 1:1 mixture of diastereoisomers at P_1, δ 8.78 (d, J = 5.5 Hz, 0.25H), 8.71 (d, J = 5.5 Hz, 0.25H), 7.88-7.60 (m, 3.5H), 6.98-6.87 (m, 1H), 4.70-4.64 (m, 0.5H), 4.22-4.09 (m, 3.5H), 1.97-1.91 (m, 3H), 1.86 (s, 3H), 1.28-1.26 (m, 1.7H), 1.09-1.07 (m, 1.3H), 0.88-0.78 (m, 18H); FAB MS m/z: 481 (MH^+); HRMS calcd for $C_{21}H_{36}F_3N_4O_5$ (MH^+) 481.2638; found: 481.2627.

Example 24.

***N*1-[(1*S*)-2-methyl-1-((1*S*)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (55, Table 2).**

This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 99%,

(system B) 99%; IR (KBr) υ 3264, 1627, 1552 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 1:1 mixture of diastereomers at P_1, δ 7.98 and 7.92 (2 x d, *J* = 7.3 and 7.3 Hz, 1H), 7.88-7.83 (m, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.58 (t, *J* = 9.4 Hz, 1H), 6.95 and 6.91 (2 x br s, 2H), 4.33-4.06 (m, 4H), 1.95 (m, 2H), 1.87 (s, 3H), 1.17-1.13 (m, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.85-0.81 (m, 6H); FAB MS m/z: 453 (MH^+), 471 (M + 19); HRMS calcd for $C_{19}H_{32}F_3N_4O_5$ (MH^+) 453.2325, found: 453.2338.

Example 25.

***N*1-[(1*S*)-2-methyl-1-((1*R*)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (56, Table 2).**

This compound was separated from **55** by preparative HPLC. HPLC (system A) 99%, (system B) 99%; IR (KBr) 1634 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 1:1 mixture of diastereomers at P_1, δ 8.63 (d, *J* = 5.5 Hz, 0.1H), 8.56 (d, *J* = 4.5 Hz, 0.1H), 8.18-8.12 (m, 0.2H), 8.01 (d, *J* = 7 Hz, 0.3H), 7.96 (d, *J* = 7.5 Hz, 0.3H), 7.89-7.74 (m, 1.8H), 7.65 (d, *J* = 9 Hz, 0.3H), 7.60 (d, *J* = 9.5 Hz, 0.3H), 6.96 -6.92 (m, 1.3H), 4.68-4.59 (m, 0.3H), 4.34-4.25 (m, 1H), 4.19-4.02 (m, 2.7H), 1.98-1.89 (m, 2H), 1.86 (s, 3H), 1.31-1.29 (m, 0.8H), 1.19-1.07 (m, 5.2H), 0.86-0.82 (m, 12H); FAB MS m/z: 453 (MH^+); HRMS calcd for $C_{19}H_{32}F_3N_4O_5$ (MH^+) 453.2325; found: 453.2338.

Example 26.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]butanediamide (57, Table 3).**

This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system D, pH 7.4) 100%; IR (KBr) υ 3283, 1642 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 19:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.05 and 8.01 (2 x d, J = 7.6 and 7.6 Hz, 1H), 7.91-7.82 (m, 2H), 7.43 and 7.39 (2 x d, J = 9.2 and 9.2 Hz, 1H), 7.01-6.80 (m, 2H), 4.61-4.52 (m, 1H), 4.22-4.00 (m, 3H), 2.94 and 2.93 (2 x s, 3H), 2.80 (s, 3H), 2.71-2.59 (m, 2H), 2.00-1.90 (m, 1H), 1.87 and 1.86 (2 x s, 3H), 1.73-1.61 (m, 1H), 1.57-1.45 (m, 1H), 1.27 and 1.26 (2 x d, J = 6.7 and 6.7 Hz, 0.15H), 1.06 (d, J = 6.0 Hz, 3H), 0.87-0.78 (m, 9H); FAB MS m/z: 510.3 (MH^+), 528.3 (M + 19); HRMS calcd for $C_{21}H_{35}F_3N_5O_6$ (MH^+) 510.2539, found: 510.2526.

Example 27.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2,2-dimethyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido-propyl)carboxamido]-butanediamide (58, Table 3).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system B) 99%; IR (KBr) υ 3500-2900, 1640, 1538 cm^{-1}; ^1H- NMR (400 MHz, DMSO-d_6), hydrated form only, 1:1 mixture of diastereomers at P_1, δ 8.20 and 8.13 (d, J = 7.4 and 7.2 Hz, 1H), 7.91 and 7.91 (d, J = 9.0 and 8.7 Hz, 1H), 7.56 and 7.55 (d, J = 9.3 and 9.3 Hz, 1H), 7.50 and 7.43 (d, J = 9.3 and 9.3 Hz, 1H), 6.93 (br s, 1H), 6.81 (br s, 1H), 4.57 (m, 1H), 4.23 (m, 2H), 4.11 (m, 1H), 2.95 and 2.94 (s, 3H), 2.80 and 2.80 (s, 3H),

2.72-2.57 (m, 2 H), 1.95 (m, J = 6.9 Hz, 1H), 1.87 (s, 3H), 1.07 and 1.06 (d, *J* = 8.1 and 6.6 Hz, 3H), 0.89 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 6H); FAB MS m/z: 538 (MH^+); HRMS calcd for $C_{23}H_{39}F_3N_5O_6$ (MH^+) 538.2852, found: 538.2843.

Example 28.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-3,3-dimethyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido butyl)carboxamido]butanediamide (59, Table 3).**

This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system D, pH 7.4) 100%; IR (KBr) υ 3285, 1644 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), 16:1 mixture of hydrate/non-hydrate, 3:2 mixture of diastereomers at P_1, δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.91-7.79 (m, 2H), 7.43 and 7.39 (2 x d, *J* = 9.2 and 9.2, 1H), 7.11-6.66 (br s, 2H hydrate), 4.62-4.49 (m, 1H), 4.36-4.25 (m, 1H), 4.16-4.02 (m, 2H), 2.94 and 2.93 (2 x s, 3H), 2.80 (s, 3H), 2.71-2.55 (m, 2H), 1.99-1.88 (m, 1H), 1.85 and 1.84 (2 x s, 3H), 1.67-1.58 (m, 1H), 1.46 (dd, *J* = 14.2 and 8.9 Hz, 1H), 1.28-1.25 (m, 0.2H), 1.06 (d, *J* = 6.7 Hz, 2.8H), 0.86 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H); FAB MS m/z: 552 (MH^+), 570 (M + 19); HRMS calcd for $C_{24}H_{41}F_3N_5O_6$ (MH^+) 552.3009, found: 552.3031.

Example 29.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(*S*)-1-(1-adamantyl)-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido**

methyl)carboxamido]butane-diamide (60, Table 3). This compound was prepared in solution using standard coupling methods and oxidized with Dess-Martin periodinane. Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system D) 99%; IR (KBr) υ 3293, 1641, 1533 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 4:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.58 (d, J = 5.5 Hz, 0.1H), 8.47 (d, J = 6.5 Hz, 0.1H), 8.22-8.12 (m, 1H), 7.94-7.91 (m, 1H), 7.49-7.38 (m, 1.9H), 6.94 (br s, 1H), 6.86 (br s, 1H), 4.60-4.52 (m, 1H), 4.24-4.20 (m, 1H), 4.13-3.98 (m, 2H), 2.94 (s, 1.5H), 2.93 (s, 1.5H), 2.79 (s, 3H), 2.74-2.57 (m, 2H), 2.00-1.94 (m, 1H), 1.94-1.86 (m, 3H), 1.87 (s, 3H), 1.64-1.48 (m, 12H), 1.26-1.25 (m, 0.6H), 1.07 (d, J = 6.5 Hz, 2.4H), 0.82 (d, J = 6.5 Hz, 6H); FAB MS m/z: 616 (MH^+); HRMS calcd for $C_{29}H_{45}F_3N_5O_6$ (MH^+) 616.3322, found: 616.3335; Anal ($C_{29}H_{44}F_3N_5O_6 \cdot H_2O$) C, H, N.

Example 30.
(3*S*)-3-((1*S*)-2-(dimethylcarbamoyl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-ethylcarbamoyl)-2,2-dimethyl-3-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropanoic acid (61, Table 3). This compound was prepared in solution using standard coupling methods. The β,β-dimethyl aspartic acid residue was incorporated as the γ-benzyl ester derivative. Oxidation of the trifluoromethyl alcohol was accomplished with the Dess-Martin periodinane. Final purification was performed by preparative HPLC. HPLC (system A) 96%, (system D) 98%, IR (KBr) υ 1654, 1532 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6)

1:1 mixture of diastereomers at P_1, δ 7.98-7.89 (m, 2 H), 7.76 (d, J = 7.5 Hz, 0.5H), 7.67 (d, J = 7.5 Hz, 0.5H), 7.53 (d, J = 9 Hz, 0.5H), 7.48 (d, J = 9 Hz, 0.5H), 6.92 (br s, 1H), 6.83 (br s, 1H), 4.75 (d, J = 9.5 Hz, 1H), 4.57-4.51 (m, 1H), 4.27-4.19 (m, 1H), 4.18-4.03 (m, 1H), 2.94 (s, 1.5H), 2.93 (s, 1.5H), 2.80 (s, 3H), 2.71-2.57 (m, 2H), 2.04-1.95 (m, 1H), 1.87 (s, 3H), 1.08-1.05 (m, 9H), 0.85 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); FAB MS m/z: 568 (MH^+); HRMS calcd for $C_{23}H_{37}F_3N_5O_8$ (MH^+) 568.2594; found: 568.2505.

Example 31.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(methylcarboxamido)propyl] carboxamidobutanediamide (62, Table 4).** This compound was prepared in solution using standard coupling methods and the trifluoromethyl alcohol oxidized with the Dess-Martin periodinane. Final purification was performed by preparative HPLC. HPLC (system A) 99%, (system E) 100%; IR (KBr) υ 1640 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of diastereomers at P_1, δ 8.06 and 7.94 (2 x d, J = 7.6 and 7.3 Hz, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.22 and 7.21 (2 x d, J = 8.9 and 9.2 Hz, 1H), 4.42-4.34 (m, 1H), 4.01 and 3.96 (2 x d, J = 8.9 and 8.9 Hz, 1H), 3.95-3.89 (m, 1H), 2.77 (d, J = 3.2 Hz, 3H), 2.62 (s, 3H), 2.59-2.42 (m, 2H), 1.72 (d, J = 3.8 Hz, 3H), 1.09 and 0.89 (2 x d, J = 7.0 and 6.7 Hz, 3H), 0.73 and 0.72 (2 x s, 9H); FAB MS m/z: 439 (MH^+), 457 (M + 19); HRMS calcd for $C_{18}H_{30}F_3N_4O_5$ (MH^+) 439.2168, found: 439.2154.

Example 32.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-1-[(4-hydroxyphenethyl)carboxamido]-2,2-dimethylpropylcarboxamido) butanediamide (63, Table 4).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed on a preparative HPLC. HPLC (system A) 97%, (system B) 95%; IR (KBr) υ 1636 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 16:1 mixture of hydrate/non-hydrate, 1.4:1 mixture of diastereomers at P_1, δ 9.20-9.00 (m, 1H), 8.23 and 8.13 (2 x d, *J* = 7.4 and 7.4 Hz, 1H), 7.79 (2 x d, *J* = 9.0 and 9.0 Hz, 1H), 7.41 (2 x d, *J* = 9.0 and 9.0 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.99-6.75 (m, 1.5H hydrate), 6.65-6.62 (m, 2H), 4.62-4.52 (m, 1H), 4.20 and 4.17 (2 x d, *J* = 9.0 and 9.0 Hz, 1H), 4.15-4.05 (m, 1H), 2.96 and 2.95 (2 x s, 3H), 2.80 (s, 3H), 2.72-2.60 (m, 4H), 2.50-2.45 (m, 1H), 2.45-2.35 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 0.1H), 1.75 (m, 2.8H), 0.86 (s, 9H); FAB MS m/z: 545 (MH^+), 563 (M+19); HRMS calcd for $C_{25}H_{36}F_3N_4O_6$ (MH^+) 545.2587, found 545.2602.

Example 33.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-1-(isobutylcarboxamido)-2,2-dimethylpropyl]carboxamidobutanediamide (64, Table 4).** This compound was prepared in solution using standard coupling methods. Final purification was performed by preparative HPLC. HPLC (system A) 95%, (system B) 99%; IR (KBr) υ 1636 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 19:1 mixture hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.21 and 8.11 (2 x d, *J* = 7.2 and 7.2 Hz, 1H), 7.73 and 7.72 (2 x d, *J* = 9.0 and 9.0 Hz, 1H), 7.44 and 7.40 (2 x d, *J* = 9.6 and 9.3 Hz, 1H),

7.1-6.7 (br, 1.7H hydrate), 4.60-4.52 (m, 1H), 4.21 and 4.19 (2 x d, J = 9.0 and 8.7 Hz, 1H), 4.15-4.04 (m, 1H), 2.96 and 2.95 (2 x s, 3H), 2.80 (s, 3H), 2.74-2.58 (m, 2H), 2.14 and 2.12 (2 x d, J = 13.2 and 12.9 Hz, 1H), 2.08 (m, 1H), 1.96 (m, 1H), 1.07-1.04 (m, 3H) 0.90 (s, 9H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); FAB MS m/z: 481 (MH^+), 499 (M+19); HRMS calcd for $C_{21}H_{36}F_3N_4O_5$ (MH^+) 481.2638, found 481.2627.

Example 34.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamidobutanediamide (65, Table 4).** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system A) 99%, (system B) 99%; IR (KBr) υ 1635 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 29:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.20 and 8.10 (2 x d, J = 7.3 and 7.0 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.44 and 7.43 (2 x d, J = 9.2 and 9.2 Hz, 1H), 6.95-6.75 (m, 1.7H), 4.56 (quintet, J = 6.7 Hz, 1H), 4.19 and 4.16 (2 x d, J = 8.9 and 8.9 Hz, 1H), 4.12-4.05 (m, 1H), 2.95 and 2.94 (2 x s, 3H), 2.79 (s, 3H), 2.75-2.60 (m, 2H), 2.20-2.15 (m, 1H), 2.04 and 2.01 (2 x d, J = 12.7 and 12.4 Hz, 1H), 1.07-1.04 (m, 3H), 0.95 (s, 9H), 0.90 (s, 9H); FAB MS m/z: 495 (MH^+), 513 (M+19); HRMS calcd for $C_{22}H_{38}F_3N_4O_5$ (MH^+) 495.2794, found 495.2777.

Example 35.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-1-[(3,3-dimethyl-butyl)amino]-**

2,2-dimethylpropylcarboxamido) butanediamide (66, Table 4). This compound was prepared by solid phase using the activated ketone resin (Example 1). The final reductive amination on the terminal *t*-butyl glycine amine (0.3 mmol) was performed on solid phase by addition of 3,3-dimethylbutyraldehyde (376 mL, 3.0 mmol) in DMF (15 mL with acetic acid (150 mL), and $NaBH_3CN$ (63 mg, 1 mmol) for 20 h. After removal of the solvent, the resin was cleaved in the usual fashion. After purification by preparative HPLC the compound was obtained as a white solid (20.6 mg) after lyophilization. HPLC (system A) 99%, (system D) 97%; IR (KBr) υ 2960, 1667 cm^{-1}; ^1H-NMR (400MHz, DMSO-d_6), 1:1 mixture of diastereomers at P_1, δ 8.79-8.72 (m, 2H), 8.04 (br s, 1H), 7.78 (d, J = 9.0 Hz, 0.5H), 7.67 (d, J = 9.0 Hz, 0.5H), 6.97-6.96 (m, 1.3H), 6.91 (s, 0.6H), 4.82-4.75 (m, 1H), 4.15-4.11 (m, 1H), 3.61 (d, J = 9.5 Hz, 1H), 2.94 (m, 3H), 2.87 (m, 1H), 2.79 (m, 3H), 2.70-2.65 (m, 3H), 1.66-1.57 (m, 1H), 1.51-1.44 (m, 1H), 1.29-1.24 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 1.02 (s, 5.4H), 0.99 (s, 3.6H), 0.89 (s, 3.6H), 0.89 (s, 5.4H); FAB MS m/z: 481 (MH^+), 499 (M + 19); HRMS calcd for $C_{22}H_{40}F_3N_4O_4$ (MH^+) 481.3002, found: 481.2991.

Example 36.

4N,4N-Dimethyl-1N-(3,3,3-trifluoro-1-methyl-2-oxopropyl-2-[1-(*tert*-butoxycarbonyl-amino)-2,2-dimethyl-(1S)-propylcarboxamido]-(2S)-butanediamide (67, Table 4). This compound was prepared on solid phase using the activated ketone resin (Example 1). The final purification was performed by preparative HPLC. HPLC (system A) 99%, (system B) 98%; IR (KBr) υ 3500-2900, 1641, 1510 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 5:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.56 (br d, J = 5.1 Hz, 0.15H), 8.10-8.00 (m, 1H), 7.50-7.46 (m, 1H), 6.93-6.82 (m, 1.7H), 6.50-6.49 (m, 1H), 4.62 (m, 1H), 4.12 (m, 1H), 3.84 (m, 1H), 2.95 (m, 3H), 2.80 (s, 3H), 2.65 (m, 2H), 1.38 (s, 9H), 1.26 (d, J = 6.6 Hz, 0.45H), 1.06 (d, J = 6.6 Hz, 2.55H), 0.88 (s, 9H); FAB MS m/z: 497 (MH^+); HRMS calcd for $C_{21}H_{36}F_3N_4O_6$ (MH^+) 497.2587, found: 497.2601.

Example 37.

***N4,N4*-Dimethyl-N1-(3,3,3-trifluoro-1-methyl-2-oxopropyl-2-[1-(tert-butylaminocarbonyl-amino)-2,2-dimethyl-(1S)-propylcarboxamido]-(2S)-butanediamide (68, Table 4).** This compound was prepared in solution using standard coupling methods and oxidation of the trifluoromethyl alcohol with the Dess-Martin periodinane. Final purification was performed by preparative HPLC. HPLC (system A) 99%, (system D) 100%; IR (KBr) υ 1641 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1:1 mixture of diastereomers at P_1, δ 8.15 and 8.09 (2 x d, J = 7.3 and 7.0 Hz, 1H), 7.51 and 7.43 (2 x d, J = 8.9 and 9.2 Hz, 1H), 6.00 (s, 1H), 5.97-5.93 (m, 1H), 4.58-4.53 (m, 1H), 4.11-4.03 (m, 1H), 3.94-3.91 (m, 1H),

2.95 (d, J = 5 Hz, 3H), 2.79 (s, 3H), 2.67-2.60 (m, 2H), 1.20 (s, 9H), 1.07-1.05 (m, 3H), 0.86 (s, 9H); FAB MS m/z: 496 (MH^+), 514 (M + 19); HRMS calcd for $C_{21}H_{37}F_3N_5O_5$ (MH^+) 496.2747, found: 496.2765.

Example 38.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-1-[(dimethylamino)methyl]carboxamido-2,2-dimethylpropyl) carboxamido]butanediamide (69, Table 4).** This compound was prepared in solution using standard coupling methods and oxidation of the trifluoromethyl alcohol with the Dess-Martin periodinane. Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system D) 98%; IR (KBr) υ 1654, 1540, 1186 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 9:1 mixture of hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 9.61 (br s, 1H), 8.68 and 8.66 (2 x d , J = 9.0 and 8.5 Hz, 1 H), 8.37 and 8.30 (2 x d, J = 7.5 and 7.0 Hz, 1H), 7.48 and 7.45 (2 x d, J = 9.0 and 9.0 Hz, 1H), 6.95-6.87 (m, 2H), 4.63-4.54 (m, 1H), 4.35-4.32 (m, 1H), 4.12-3.94 (m, 3H), 2.95-2.94 (m, 3H), 2.95-2.94 (m, 3H), 2.80-2.78 (m, 9H), 2.72-2.56 (m, 2H), 1.26-1.24 (m, 0.3H), 1.07-1.06 (m, 2.7H), 0.92 (s, 9H); FAB MS m/z: 482 (MH^+), 500.1 (M + 19); HRMS calcd for $C_{20}H_{35}F_3N_5O_5$ (MH^+) 482.2590, found: 482.2599.

Example 39.

4-[(1*S*)-1-((1*S*)-2-(dimethylcarbamoyl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl] ethylcarbamoyl)-2,2-dimethylpropyl]carbamoylbutanoic acid (70, Table 4). This compound was prepared in solution using standard coupling methods. The final P_4

residue was introduced by the opening of glutaric anhydride in Et_3N. Final purification was performed by preparative HPLC. HPLC (system A) 100%, (system D) 100%; IR (KBr) υ 1638, 1537, 1176 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) 1:1 mixture of diastereomers at P_1, δ 8.22 and 8.12 (2 x d, *J* = 7.5 and 7.0 Hz, 1H), 7.81-7.72 (m, 1H), 7.43 and 7.39 (2 x d, *J* = 9.0 and 9.0 Hz, 1H), 6.93 (br s, 0.8H), 6.81 (br s, 0.8H), 4.60-4.52 (m, 1H), 4.21-4.18 (m, 1H), 4.12-4.05 (m, 1H), 2.95-2.94 (m, 3H), 2.79 (s, 3H), 2.68-2.63 (m, 2H), 2.28-2.14 (m, 4H), 1.73-1.66 (m, 2H), 1.11-1.05 (m, 3H), 0.89 (s, 9H); FAB MS m/z: 511.2 (MH^+), 529 (M + 19); HRMS calcd for $C_{21}H_{34}F_3N_4O_7$ (MH^+) 511.2379, found: 511.2363; Anal ($C_{21}H_{33}F_3N_4O_7 \cdot 2H_2O$) C, H, N.

Example 40.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-1-amino-2,2-dimethylpropyl] carboxamidobutanediamide.** This compound was prepared on solid phase using the activated ketone resin (Example 1). Final purification was performed by preparative HPLC. HPLC (system D) 99%, (system E) 99%; IR (KBr) υ 1670 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 2:1 hydrate/non-hydrate, 1:1 mixture of diastereomers at P_1, δ 8.87 and 8.80 (2 x d, *J* = 5.7 and 6.4 Hz, 0.4H), 8.56-8.49 (m, 1H), 8.02 (br s, 3H), 7.69 and 7.64 (2 x d, *J* = 9.0 and 9.2 Hz, 0.6H), 6.96, 6.95, 6.88 and 6.83 (4 x s, 1.3H), 4.73-4.63 (m, 1.4H), 4.14-4.08 (m, 0.6H), 3.55-3.48 (m, 1H), 2.96 (s, 3H), 2.82 (s, 3H), 2.74-2.58 (m, 2H), 1.25 (d, *J* = 6.7 Hz, 1H), 1.08 and 1.07 (2 x d, *J* = 6.7 and 6.7 Hz, 2H), 1.01-0.96 (m, 9H); FAB MS m/z: 397 (MH^+), 415 (M + 19); HRMS calcd for $C_{16}H_{28}F_3N_4O_4$ (MH^+) 397.2063, found: 397.2077.

Example 41.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-1-hydroxy-2,2-dimethylpropyl] carboxamidobutanediamide.** This compound was prepared in solution using standard coupling methods. The 2-hydroxy isobutyric acid moiety was introduced as the acetyl derivative. Oxidation of the trifluoromethyl alcohol with the Dess-Martin periodinane was followed by cleavage of the acetate group with aq. NaOH. Final purification was performed by preparative HPLC. HPLC (system A) 92%, (system D) 99%; IR (KBr) υ 1641 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 2:1 hydrate, non-hydrate, 1:1 mixture of diastereomers at P_1, δ 7.83 and 7.79 (2 x d, J = 7.9 and 7.6 Hz, 1H), 7.73-7.67 (m, 0.3H), 7.57 and 7.52 (2 x d, J = 9.2 and 9.2 Hz, 1H), 7.04-6.82 (m, 2H, hydrate), 5.69-5.47 (m, 1H), 4.65-4.55 (m, 1H), 4.19-4.05 (m, 1H), 2.95 and 2.94 (2 x s, 3H) 2.80 and 2.79 (2 x s, 3H), 2.79-2.53 (m, 3H), 1.39-1.02 (m, 3H), 0.87 (s, 9H); FAB MS m/z: 398 (MH^+), 416 (M+19); HRMS calcd. for $C_{16}H_{27}F_3N_3O_5$ (MH^+) 398.1903, found: 398.1892.

Example 42.

***N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-(neopentylcarboxamido)-butanediamide.** This compound was prepared in solution using standard coupling methods and final oxidation of the trifluoromethyl alcohol was accomplished with the Dess-Martin periodinane. Final purification was performed by preparative HPLC. HPLC (system D) 97%, (system E) 99%; IR (KBr) υ 1638 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 2:1 mixture of diastereomers at P_1, δ 7.80-7.77 (m, 1H), 7.27 and 7.22 (2 x d, J = 9.2 and 9.2 Hz, 1H), 4.49-

4.42 (m, 1H), 3.98-3.92 (m, 1H), 2.80 (s, 3H), 2.64 (s, 3H), 2.55-2.40 (m, 2H), 1.84 (s, 2H), 1.10 and 0.92 (2 x d, J = 6.9 and 6.6 Hz, 3H), 0.79 (s, 9H); FAB MS m/z: 382 (MH^+), 400 (M + 19); HRMS calcd for $C_{16}H_{27}F_3N_3O_4$ (MH^+) 382.1954, found: 382.1968.

Example 43.

***N*4,*N*4-dimethyl-*N*1-(3,3,4,4,4-pentafluoro-1-methyl-2-oxobutyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentyl carboxamido)propyl]carboxamidobutanediamide (74, Table 5).** Compound **11** (0.92 g, 3.14 mmol) was treated with 4 N HCl/dioxane (1.5 h) before being concentrated *in vacuo*. The resulting hydrochloride salt (3.14 mmol) was combined with Boc-Asn(γ-NMe_2)-OH (0.93 g, 3.45 mmol), TBTU (1.21 g, 3.77 mmol), HOBt (0.51 g, 1.2 mmol), and *i*-Pr_2NEt (1.64 mL, 9.42 mmol) in CH_2Cl_2 (10 mL). After 3 h at rt, the mixture was extracted into EtOAc and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (4:1 EtOAc/hexane) to give the coupled product (0.594 g, 43 %). HPLC (system A) 93%; ^{1}H-NMR ($CDCl_3$), 1.3:1 mixture of diastereomers, δ 6.92 (bs, 0.6H) , 6.66 (d, J = 7.95 Hz, 0.4H), 5.80 (m, 1H), 4.71 (bs, 0.4H), 4.50 (m, 1.6H), 4.45-4.20 (m, 2H), 3.34 (dd, J = 16.85 and 16.85 Hz, 0.4H), 3.06-2.97(m, 0.6H), 3.045 and 3.04 (2 x s, 3H), 3.02 and 3.00 (2 x s, 3H), 2.67 (dd, J = 7.63 and 7.63 Hz, 0.6H), 2.58 (dd, J = 16.85 and 16.85 Hz, 0.4H), 1.48 and 1.46 (2 x s, 9H), 1.32 (t, J = 7.95 Hz, 3H). The dipeptide (0.43 g, 0.99 mmol) was treated with 4 N HCl/dioxane (10 mL) for 2 h before being concentrated *in vacuo*. The resulting hydrochloride salt (0.99 mmol) was combined

with Boc-Tbg-OH (0.254 g, 1.1 mmol), BOP (0.487 g, 1.1 mmol), and *i*-Pr_2NEt (0.52 mL, 3.0 mmol) in CH_2Cl_2 (10 mL). After 2.5 h at rt, the mixture was extracted into EtOAc and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1 EtOAc/hexane) to give the coupled product as a white solid (0.33 g, 60%). HPLC (system A) 99%; ^1H-NMR ($CDCl_3$), 1.3:1 mixture of diastereomers, δ 8.15 (m, 0.4H), 7.73 (m, 0.6H), 7.37 (m, 0.6H), 7.10 (m, 0.4H), 5.12 (m, 1H), 4.77 (m, 0.7H), 4.69 (m, 1.3H), 4.25 (m, 2H), 3.76 (m, 1H), 3.26 (dd, *J* = 15.9 and 15.9 Hz, 0.4H), 3.16 (dd, *J* = 12.4 and 12.4 Hz, 0.6H), 3.06 and 3.03 (2 x s, 3H), 2.94 and 2.92 (2 x s, 3H), 2.55 (dd, *J* = 7.0 and 7.0 Hz, 0.6H), 2.39 (dd, *J* = 11.4 and 11.4 Hz, 0.4H), 1.46 and 1.45 (2 x s, 9H), 1.37-1.25 (m, 3H), 1.06 and 1.03 (2 x s, 9H). This peptide (0.30 g, 0.67 mmol) was then treated with 4 N HCl/dioxane (10 mL) and concentrated *in vacuo*. The hydrochloride salt was combined with *tert*-butylacetic acid (0.094 µL, 0.74 mmol), BOP (0.33 g, 0.74 mmol), *i*-Pr_2NEt (0.23 mL, 1.34 mmol) in CH_2Cl_2 (10 mL) and stirred 3.5 h at rt. The mixture was diluted with EtOAc and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired peptide as a white solid (0.297 g, 88%). HPLC (system A) 99%); ^1H-NMR ($CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.32 (d, 8.3 Hz, 1H), 6.18 (d, *J* = 6.7 Hz, 1H), 5.21 (d, *J* = 6.7 Hz, 1H), 4.82-4.78 (m, 1H), 4.39-4.31 (m, 1H), 4.23-4.10 (m, 2H), 3.11-3.06 (dd, *J* =

16.2 and 15.7 Hz, 1H), 2.99 (s, 3H), 2.91 (s, 3H), 2.52 (dd, J = 16.2 and 15.9 Hz, 1H), 2.18 (s, 2H), 1.27 (d, J = 6.7 Hz, 3H), 1.06 (s, 9H), 1.05 (s, 9H). The alcohol (0.26 g, 0.48 mmol) so obtained was combined with Dess-Martin periodinane (0.51 g, 1.19 mmol) in CH_2Cl_2 (5 mL) and stirred for 4 h. The reaction mixture was diluted with EtOAc and treated with a 1:1 mixture of 10% $Na_2S_2O_3$: saturated $NaHCO_3$ (10 mL) for 15 min. After extraction with EtOAc the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The pentafluoroethyl ketone was obtained by trituration with 3:1 hexane/EtOAc to give **74** as a white solid (0.217 g, 84%). IR (KBr) υ 1685, 1618 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 3:1 mixture of diastereomers at P_1, δ 8.20 and 8.14 (2 x d, J = 7.5 and 7.5 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 6.91 (m, 2H), 4.58 (m, 1H), 4.16 (m, 2H), 2.95 and 2.80 (2 x s, 6H), 2.70 (m, 2H), 2.11 (m, 2H), 1.08 (d, J = 6.6 Hz, 3H), 0.95 (s, 9H), 0.91 (s, 9H); HRMS calcd for $C_{23}H_{38}F_5N_4O_5$ (MH^+) 545.2762, found: 545.2775.

Example 44.

_N_1-[3-(benzylcarbamoyl)-3,3-difluoro-1-methyl-2-oxopropyl]-_N_4,_N_4-dimethyl-(2_S_)-2-[(1_S_)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamidobutane diamide (75, Table 5).

Compound **13** (0.263 g, 0.73 mmol) was treated with 4N HCl/dioxane (6 mL) for 30 min before being concentrated *in vacuo*. The resulting hydrochloride salt was combined with BOP (0.39 g, 0.88 mmol), Boc-Asn(γ-NMe_2)-OH (0.191 g, 0.73 mmol) and i-Pr_2NEt (0.32 mL, 1.83 mmol) in CH_2Cl_2 (5 mL). After 4 h, the reaction was poured into

EtOAc and washed sequentially with 1N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The material was trituated with 3:7 hexane:EtOAc to give a white solid (0.30 g, 82%). ^{1}H-NMR ($CDCl_3$) δ 7.41-7.28 (m, 6H), 6.98-6.94 (m br, 1H), 5.56-5.51 (m br, 1H), 4.59-4.42 (m, 4H), 4.11-4.03 (m, 2H), 3.11-3.05 (m, 1H), 2.99 (s, 3H), 2.88 (s, 3H), 2.61-2.54 (m, 1H), 1.45 (s, 9H), 1.32 (d, J = 6.6 Hz, 3H). This material (0.27 g, 0.54 mmol) was treated with 4 N HCl/dioxane (6 mL) for 30 min before being concentrated *in vacuo*. The hydrochloride salt (0.54 mmol) was combined with Boc-Tbg-OH (0.125 g, 0.54 mmol), BOP (0.286 g, 0.65 mmol) and *i*-Pr_2NEt (0.23 mL, 1.35 mmol) in CH_2Cl_2 (3 mL) and stirred for 4 h. The mixture was diluted with EtOAc and washed sequentially with 1 N HCl, saturated aqueous $NaHCO_3$, and brine before being dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by flash chromatography using TLC grade silica gel to afford a white solid (0.25 g, 76%). ^{1}H-NMR ($CDCl_3$) δ 8.06 (s br, 1H), 7.68 (s br, 1H), 7.33-7.26 (m, 6H), 5.11 (d, J = 4.4 Hz, 1H), 4.67 (dd, J = 14.6, 7.0 Hz, 1H), 4.50 (s br, 1H), 4.32-4.22 (m, 3H), 4.13-4.07 (m, 1H), 3.71 (d, J = 5.7 Hz, 1H), 3.23-3.20 (m, 1H), 3.00 (s, 3H), 2.87 (s, 3H), 2.43-2.38 (dd, J = 15.9, 5.7 Hz, 1H), 1.49 (s, 9H), 1.22 (d, J = 6.7 Hz, 3H), 1.02 (s, 9H). This peptide (0.25 g, 0.41 mmol) was treated with 4 N HCl/dioxane (3 mL) and stirred 1 h before being concentrated *in vacuo*. The hydrochloride salt (0.41 mmol) was combined with *tert*-butylacetic acid (52 µL, 0.41 mmol), BOP (0.216 g, 0.49 mmol) and *i*-Pr_2NEt (0.18 mL, 1.02 mmol) in CH_2Cl_2 (3 mL) and stirred 4 h. The

mixture was diluted with EtOAc and washed sequentially with 1 N HCl, saturated aqueous $NaHCO_3$, and brine before being dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by flash chromatography using TLC grade silica gel (5% MeOH/EtOAc) to give the fully elaborated peptide as a white solid (0.191 g, 77%). ^{1}H-NMR ($CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.37-7.27 (m, 7H), 5.97 (d, J = 6.7 Hz, 1H), 4.65-4.59 (m, 2H), 4.46 (d, J = 9.2 Hz, 1H), 4.35 (dd, J = 15.0, 5.4 Hz, 1H), 4.28-4.24 (m, 1H), 4.15-4.06 (m, 1H), 4.02 (d, J = 6.7 Hz, 1H), 3.16 (dd, J = 15.9, 3.5 Hz, 1H), 2.99 (s, 3H), 2.87 (s, 3H), 2.45 (dd, J = 15.6, 9.2 Hz, 1H), 2.19 (dd, J = 18.1, 13.0 Hz, 2H), 1.24 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 1.03 (s, 9H). The peptide (0.15 g, 0.245 mmol) was dissolved in CH_2Cl_2 (15 mL) and treated with Dess-Martin periodinane (0.10 g, 0.245 mmol) and stirred at rt for 5 h. The mixture was diluted with EtOAc and treated with a 1:1 mixture of 10 % $Na_2S_2O_3$: saturated $NaHCO_3$ (15 min). The organic phase was washed sequentially with saturated $NaHCO_3$, 10% citric acid, and brine before being dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The final product was purified by preparative HPLC to give, after lyophilization, compound 75 as a white solid (0.115 g, 77%). IR (KBr) υ 3293, 1680, 1635 cm^{-1}, ^{1}H-NMR ($CDCl_3$), 1:3 mixture of hydrate/non-hydrate, δ 9.65-9.55 (m, 0.25H), 8.99-8.47 (m, 0.75H), 8.20-8.15 (m, 1H), 7.65-7.55 (m, 1H), 7.40-7.20 (m, 6H), 6.55 (br s, 0.25H), 6.34 (br s, 0.75H), 4.80-4.72 (m, 0.25H), 4.59-4.53 (m, 1H), 4.42-4.26 (m, 2H), 4.26-4.16 (m, 1.5H), 4.11 (d, *J* = 8.3 Hz, 0.25), 2.96 (s, 2.25H), 2.93 (s, 0.75H), 2.79 (s, 0.75H), 2.77 (s,

2.25H), 2.68 (m, 2H), 2.25-2.18 (m, 1H), 2.05-1.95 (m, 1H), 1.24 (d, J = 7.0 Hz, 0.75H), 1.06 (d, J = 6.6 Hz, 2.25H), 0.95 (s, 9H), 0.90 (s, 9H); ^{13}C-NMR (100.6 MHz, DMSO-d_6) δ 197.32, 197.06, 196.79, 171.46, 171.08, 170.98, 170.49, 170.33, 169.86, 169.34, 161.15, 160.88, 160.62, 138.54, 138.04, 128.53, 128.40, 127.43, 127.27, 127.21, 126.98, 112.32, 109.68, 107.04, 60.45, 59.80, 50.04, 49.87, 49.58, 48.44, 48.26, 42.60, 42.36, 36.81, 35.03, 34.28, 33.89, 30.74, 29.84, 26.83, 15.54; HRMS calcd for $C_{30}H_{46}F_2N_5O_6$ (MH^+) 610.3416, found: 610.3395.

Example 45.

***N*1-[2-(1,3-benzoxazol-2-yl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl -1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (77, Table 5).** A mixture of **16** (265 mg, 0.81 mmol) and 10% Pd on carbon (79 mg) in ethanol (20 mL) was stirred under an atmosphere of hydrogen for 1 h. The solution was then filtered through a glass microfiber and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (6 mL) and Boc-Asn(γ-NMe_2)-OH (222 mg, 0.85 mmol), HOBt (220 mg, 1.63 mmol), i-Pr_2NEt (0.56 mL, 3.25 mmol) and EDC (169 mg, 0.88 mmol) were added. Additional i-Pr_2NEt was introduced to bring the pH above 8 and stirring was continued overnight. The resulting mixture was diluted with EtOAc and washed sequentially with 10 % citric acid, 10% Na_2CO_3 and water and dried by passing through a plug of glass wool. Flash chromatography (EtOAc) gave the desired compound (314 mg, 95%) ^{1}H-NMR (DMSO-d_6) δ 7.82-7.66 (m, 3H), 7.42-7.33 (m, 3H), 6.78 and 6.73 (2 x d, J = 7.8 and 7.5 Hz, 1H), 6.23-6.18 and 6.16-6.11 (2 x m, 1H),

4.84-4.82 and 4.66-4.50 (2 x m, 1H), 4.33-4.17 (m, 2H), 2.88, 2.77, 2.74 (3 x s, 6H), 2.58-2.20 (m, 2H), 1.34 (s, 9H), 1.18-1.15 (m, 3H). This product was stirred in a mixture of CH_2Cl_2 (8 mL) and TFA (2 mL) for 2 h. After removal of the solvent, residual TFA was removed by azeotropic distillation with benzene using a rotary evaporator. The residue was dissolved in CH_2Cl_2 (6 mL) and Boc-Tbg-OH (188 mg, 0.81 mmol), HOBt (209 mg, 1.55 mmol), *i*-Pr_2NEt (0.54 mL, 3.10 mmol) and EDC (161 mg, 0.84 mmol) were added. Additional *i*-Pr_2NEt was introduced to bring the pH above 8 and stirring was continued overnight. The resulting mixture was diluted with EtOAc and washed sequentially with 10 % citric acid, 10% Na_2CO_3 and water and dried by passing through a plug of glass wool. Flash chromatography (EtOAc) gave the desired compound (264 mg, 62%). ^{1}H-NMR (DMSO-d_6) δ 7.89-7.82 and 7.73-7.68 (m, 4H), 7.42-7.33 (m, 2H), 6.45 (d, J = 6.9 Hz, 1H), 6.19 and 6.06 (2 x d, J = 6.0 and 5.4 Hz, 1H), 4.84 and 4.68 (2 x t, J = 5.1 and 6.3 Hz, 1H), 4.61-4.51 (m, 1H), 4.33-4.23 (m, 1H), 3.84-3.77 (m, 1H), 2.89, 2.78, 2.72 (3 x s, 6H), 2.58-2.27 (m, 2H), 1.38 (s, 9H), 1.12 (m, 3H), 0.86 and 0.84 (2 x s, 9H). This product was stirred in a mixture of CH_2Cl_2 (8 mL) and TFA (2 mL) for 2 h. After removal of the solvent, residual TFA was removed by azeotropic distillation with benzene using a rotary evaporator. The residue was dissolved in CH_2Cl_2 (6 mL) and *tert*-butylacetic acid (64 mg, 0.50 mmol), HOBt (129 mg, 0.96 mmol), *i*-Pr_2NEt (0.33 mL, 1.91 mmol) and EDC (99 mg, 0.52 mmol) were added. Additional *i*-Pr_2NEt was introduced to bring the pH above 8 and stirring was continued overnight. The resulting mixture was diluted

with EtOAc and washed sequentially with 10 % citric acid, 10% Na_2CO_3, water and dried by passing through a plug of glass wool. Flash chromatography (EtOAc) gave the desired compound (162 mg, 62%) which was immediately dissolved in CH_2Cl_2 (8 mL). Dess-Martin periodinane (252 mg, 0.59 mmol) was added and the resulting mixture stirred for 1 h. A 1:1 mixture of 10 % $Na_2S_2O_3$: saturated $NaHCO_3$ was introduced and stirring was continued until both layers were clear (10 min). The residue was extracted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography using TLC grade silica gel (3 % ethanol in EtOAc) afforded the compound as a colorless oil. This material was dissolved in a minimum amount of CH_3CN, diluted with water and lyophilized to afford the desired compound **77** as a white solid (99.3 mg, 61 %). IR (KBr) υ 3311, 1713, 1657 cm^{-1}; ^1H-NMR (DMSO-d_6), 2.7:1 mixture of diastereomers, δ 8.28 (d, J = 5.7 Hz, 1H), 8.16 and 8.08 (2 x d, *J* = 7.5 and 7.5 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 7.75-7.53 (m, 2H), 7.45-7.34 (m, 1H), 6.99 and 6.75 (2 x s, 1H, hydrate), 5.30-5.22 and 4.41-4.35 (2 x m, 1H), 4.62 and 4.52 (2 x q, *J* = 6.0 and 7.2 Hz, 1H), 4.18 and 4.13 (2 x d, *J* = 9.0 and 8.4 Hz, 1H), 2.91 and 2.82 (2 x s, 3H), 2.77 and 2.71 (2 x s, 3H), 2.73-2.59 (m, 2H), 2.20 and 2.16 (2 x d, J_{AB} = 12.6 and 12.9 Hz, 1H), 2.03 and 2.02 (2 x d, J_{AB} = 12.6 and 12.9 Hz, 1H), 1.42 and 1.06 (d, *J* = 7.2 and 6.9 Hz, 3H), 0.95-0.87 (m, 18H); HRMS calcd for $C_{28}H_{42}N_5O_6$ (MH^+) 544.3135, found: 544.3154; Anal ($C_{28}H_{41}N_5O_6$) C, H, N.

Example 46.

Diphenyl *N*4,*N*4-dimethyl-*N*1-(1-aminoethylphosphinate)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (79, Table 5). To a warm solution of 1-(N-Benzyloxycarbonyl)-aminoethylphosphonate (Oleksyszyn, J.; Subotkowska, L.; Mastalerz, P. Diphenyl 1-aminoalkanephosphonates. *Synthesis*, 1979, 985-986) (8.50 g, 21.0 mmol) in ethanol (75 mL) was added a solution of 4 N HCl/dioxane (5.25 mL, 21.0 mmol) and 10% Pd/C (850 mg, 10% w/w). The mixture was stirred vigorously, flushed three times with hydrogen and stirred 16 h under a hydrogen atmosphere (balloon). The catalyst was filtered through Celite and the filtrate concentrated *in vacuo*. The residual oil was triturated in Et_2O (150 mL) until a white solid was obtained. This was filtered and dried to give 6.10 g (93%) of the corresponding hydrochloride salt. ^{1}H-NMR (DMSO-d_6) δ 9.18 (s, 3H), 7.40-7.44 (m, 4H), 7.24-7.27 (m, 6H), 4.18 (dt, J = 7.2, 20.3 Hz, 1H), 1.61 (dd, J_1 = 7.2 Hz, J_2 = 18.0 Hz, 3H). A stirred solution containing Boc-Asn(γ-NMe_2)-OH (500 mg, 1.92 mmol), the hydrochloride salt from above (663 mg, 2.11 mmol), *i*-Pr_2NEt (836 µL, 4.80 mmol) and TBTU (677 mg, 2.11 mmol) in DMF (8 mL) was stirred initially at 0 °C for 15 min, and then at rt for 3 h under an atmosphere of nitrogen. The solution was poured into brine and the product extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed sequentially with 5% aqueous $NaHCO_3$, 1 M citric acid, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 0.975 g of an amorphous solid. The product was

purified by flash chromatography (gradient 15-30% *i*-PrOH/hexane) to yield the coupled phosphonate derivative as an amorphous solid (0.81 g, 81%). HPLC (system A) 99.5%; ^{1}H-NMR ($CDCl_3$) 1:1 mixture of diastereomers at P_1, δ 7.65-7.35 (m, 1H), 7.30-7.05 (m, 10H), 6.20-5.95 (m, 1H), 4.86-4.64 (m, 1H), 4.54-4.42 (m, 1H), 3.16-3.05 (m, 1H), 2.97-2.74 (m, 6H), 2.56-2.41 (m, 1H), 1.55-1.45 (m, 3H), 1.38 (s, 9H); FAB MS m/z : 520 (MH^+), 420 (MH^+ - 100). This material (0.75 g, 1.44 mmol) was treated with 4 N HCl/dioxane (30 min) before being concentrated *in vacuo*. The hydrochloride salt (1.44 mmol) was combined with Boc-Tbg-OH (0.40 g, 1.73 mmol), TBTU (0.555 g, 1.73 mmol) and *i*-Pr_2NEt (1.05 mL, 6.05 mmol) in DMF (8 mL) initially at 0 °C (15 min) and then at rt 16 h. The reaction mixture was diluted with EtOAc and washed sequentially with 5% aqueous $NaHCO_3$, 1 M citric acid, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography using TLC grade silica gel (20% *i*-PrOH/hexane) gave the desired dipeptide fragment as a white solid (0.773 g, 85%). ^{1}H-NMR ($CDCl_3$) δ 8.06-7.80 (m, 1H), 7.50-7.40 (m, 1H), 7.38-7.10 (m, 10H), 5.24-5.12 (m, 1H), 4.86-4.68 (m, 2H), 3.84-3.76 (m, 1H), 3.21-3.07 (m, 1H), 2.95-2.78 (m, 6H), 2.58-2.35 (m, 1H), 1.61-1.49 (m, 3H), 1.43 (s, 9H), 0.96 (s, 9H); FAB MS m/z: 633 (MH^+), 533 (MH^+ - 100). This compound (0.70 g, 1.0 mmol) was treated with 4 N HCl/dioxane (30 min) before being concentrated *in vacuo*. The hydrochloride salt (1.0 mmol) was combined with *tert*-butylacetic acid (191 µL, 1.50 mmol), TBTU (0.385 g, 1.20 mmol) and *i*-Pr_2NEt (0.52 mL, 3.0 mmol) in DMF (10 mL) for 16 h. The reaction mixture was

diluted with EtOAc and washed sequentially with 5% aqueous $NaHCO_3$, 1 M citric acid, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification was performed by preparative HPLC to give compound **79** (155 mg, 25%). IR (KBr) υ 3289, 1642 cm^{-1}; ^1H-NMR (DMSO-d_6), 2:1 mixture of diastereomers at P_1, δ 8.35 (d, *J* = 8.9 Hz, 0.34H), 8.24 (d, *J* = 7.3 Hz, 0.66H), 8.20 (d, *J* = 9.2 Hz, 0.66H), 8.15 (d, *J* = 7.6 Hz, 0.34H), 7.63 (d, *J* = 8.6 Hz, 0.66H), 7.58 (d, *J* = 8.6 Hz, 0.34H), 7.33-7.40 (m, 4H), 7.14-7.23 (m, 6H), 4.57-4.72 (m, 2H), 4.18 (d, *J* = 8.6 Hz, 0.66H), 4.17 (d, *J* = 8.6 Hz, 0.34H), 3.62 (s, broad, 1H), 2.94 (s, 1H), 2.88 (s, 2H), 2.79 (s, 1H), 2.77 (s, 2H), 2.59-2.74 (m, 1H), 2.20 (d, *J* = 12.7 Hz, 0.66H), 2.17 (d, *J* = 12.7 Hz, 0.34H), 2.02 (d, *J* = 12.7 Hz, 0.66H), 1.98 (d, *J* = 12.7 Hz, 0.34H), 1.44 (d, *J* = 7.3 Hz, 1.5H), 1.39 (d, *J* = 7.3 Hz, 1.5H), 0.95 (s, 5.9H), 0.92 (s, 5.9H), 0.91(s, 3.1H), 0.88 (s, 3.1H); HRMS calcd for $C_{32}H_{48}N_4O_7P$ (MH^+) 631.3260, found: 631.3279; Anal ($C_{32}H_{47}N_4O_7P$) C, H, N.

Example 47.
***N*1-[2-(1,3-benzothiazol-2-yl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-di-methyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (80, Table 5).** This compound was prepared from **14** using standard coupling methods and oxidation of the heterocyclic alcohol with the Moffatt-Pfitzner method. Final purification was performed by preparative HPLC. HPLC (system A) 99%, (system D) 100%; IR (KBr) υ 1642 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 1.5:1 mixture of diastereomers, δ 8.30-8.13 (m, 4H), 7.73-7.58 (m, 3H),

5.47-5.38 (m, 1H), 4.68-4.60 (m, 1H), 4.18-4.10 (m, 1H), 2.92 (s, 3H), 2.79 (s, 3H), 2.76-2.63 (m, 2H), 2.20 (d, J = 12.5 Hz, 1H), 2.03 (d, J = 12.5 Hz, 1H), 1.43 and 1.37-1.28 (d, J = 7.3 Hz; m, 3H), 0.95 (s, 9H), 0.90 (s, 9H); FAB MS m/z: 560 (MH^+); HRMS calcd for $C_{28}H_{42}N_5O_5S$ (MH^+) 560.2906, found: 560.2896.

Example 48.

***N*4,*N*4-dimethyl-*N*1-(1-methyl-2-[1,3]oxazolo[4,5-*b*]pyridin-2-yl-2-oxoethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (81, Table 5).** This compound was prepared from **17** using standard coupling methods and oxidation of the heterocyclic alcohol with the Dess-Martin periodinane. Final purification was performed by preparative HPLC. 1 : 1 mixture of isomers; HPLC (system A) 97%, (system D) 98%; IR (KBr) υ 1703, 1682, 1643 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 11.39 and 11.30 (2 x s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 7.96-7.83 (m, 1H), 7.63-7.56 (m, 2H), 7.39-7.32 (m, 2H), 7.06-6.95 (m, 1H), 4.65-4.46 (m, 2H), 4.25 and 4.22 (2 x d, J = 9.1 and 8.3 Hz, 1H), 2.95 and 2.91 (2 x s, 3H), 2.77 and 2.66 (2 x s, 3H), 2.72-2.45 (m, 2H), 2.18-2.00 (m, 2H), 1.17 and 1.10 (2 x d, J = 6.8 and 6.8 Hz, 3H), 0.98-0.85 (m, 18H); FAB MS m/z: 563 (M + 19), 585 (M + 18 + 23); HRMS calcd for $C_{27}H_{43}N_6O_7$ (M+19) 563.3193, found: 563.3207.

Example 49.

***N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(6-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (82, Table 5).** This compound was prepared from **20** using

standard coupling methods and oxidation of the heterocyclic alcohol with the Dess-Martin periodinane. Final purification was performed by radial chromatography. HPLC (system A) 97%, (system C) 100%, (system D) 96%; IR (KBr) υ 1713, 1650, 1642 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6), 5:1 mixture of diastereomers, δ 8.36 and 8.15 (2 x d, J = 8.4 and 7.2 Hz, 1H), 8.31 and 8.25 (2 x d, J = 5.1 and 5.7 Hz, 1H), 7.89-7.86 (m, 1H), 7.73-7.69 (m, 1H), 7.63-7.51 (m, 1H), 7.41-7.36 (m, 1H), 5.29-5.21 and 4.74-7.68 (2 x m, 1H), 4.67-4.50 (m, 1H), 4.14 and 3.91 (2 x d, J = 8.7 and 6.0 Hz, 1H), 2.93-2.58 (m, 8H), 2.49 (s, 3H), 2.23-2.18 (m, 1H), 2.05-2.01 (m, 1H), 1.45 and 1.41 (2 x d, J = 7.2 and 7.2 Hz, 3H), 0.97-0.87 (m, 18H); FAB MS m/z: 558 (MH^+); HRMS calcd for $C_{29}H_{44}N_5O_6$ (MH^+) 558.3292, found: 558.3307; Anal ($C_{28}H_{43}N_5O_6 \cdot \frac{1}{2}H_2O$) C, H, N.

Example 50.
***N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(5-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (83, Table 5).** This compound was prepared from **19** using standard coupling methods and oxidation of the heterocyclic alcohol with the Dess-Martin periodinane. Final purification was performed by flash chromatography. HPLC (system A) 96%, (system C) 99%, (system D) 94%; IR (KBr) υ 1713, 1642 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 1.7:1 mixture of diastereomers, δ 8.38-8.06 (m, 2H), 7.81-7.67 (m, 2H), 7.63-7.37 (m, 2H), 5.28-5.20 and 4.73-4.67 (2 x m, 1H), 4.62 and 4.55-4.48 (q, J = 7.2 Hz; m, 1H), 4.13 and 3.91 (2 x d, J = 8.4 and 6.3 Hz, 1H), 2.93-2.46 (m, 8H), 2.49 (s, 3H), 2.21 and 2.20 (2 x d, J_{AB} = 12.3 and 12.4 Hz, 1H), 2.03 (2 x d, J_{AB} = 12.3 Hz, 1H), 1.45 and 1.41 (2 x d, J = 7.2 and 7.2 Hz, 3H), 0.97-0.87 (m, 18H); FAB MS m/z: 558 (MH^+); HRMS calcd for $C_{29}H_{44}N_5O_6$ (MH^+) 558.3292, found: 558.3307; Anal ($C_{29}H_{43}N_5O_6 \cdot \frac{1}{2}H_2O$) C, H, N.

Example 51.
***N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(4-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (84, Table 5).** This compound was prepared from **18** using standard coupling methods and oxidation of the heterocyclic alcohol with the Dess-Martin periodinane. Final purification was performed by flash chromatography. HPLC (system A) 97%, (system C) 99%, (system D) 94%; IR (KBr) υ 1713, 1658, 1642 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 4:1 mixture of diastereomers, δ 8.38-8.08 (m, 2H), 7.71-7.15 (m, 4H), 5.32-5.24 and

4.74-4.68 (2 x m, 1H), 4.63 and 4.55 (2 x q, J = 6.3 and 6.6 Hz, 1H), 4.14 and 3.91 (2 x d, J = 8.4 and 6.6 Hz, 1H), 2.93-2.48 (m, 11H), 2.20 (d, J_{AB} = 12.6 Hz, 1H), 2.03 (d, J_{AB} = 12.6 Hz, 1H), 1.45 and 1.42 (2 x d, J = 7.2 and 7.2 Hz, 3H), 0.97-0.87 (m, 18H); FAB MS m/z: 558 (MH^+); HRMS calcd for $C_{29}H_{44}N_5O_6$ (MH^+) 558.3292, found: 558.3307; Anal ($C_{29}H_{43}N_5O_6 \cdot \frac{1}{2}H_2O$) C, H, N.

Example 52.

***N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(7-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (85, Table 5).** This compound was prepared from **21** using standard coupling methods and oxidation of the heterocyclic alcohol with the Dess-Martin periodinane. Final purification was performed by flash chromatography. HPLC (system A) 97%, (system C) 97%, (system D) 92%; IR (KBr) υ 1715, 1642 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), 4:1 mixture of diastereomers, δ 8.37 and 8.15 (2 x d, J = 8.1 and 7.5 Hz, 1H), 8.34 and 8.28 (2 x d, J = 5.9 and 5.7 Hz, 1H), 7.83-7.20 (m, 4H), 5.26 and 4.73-4.68 (quint, J = 6.3 Hz; m, 1H), 4.62 and 4.57 (2 x q, J = 6.0 and 6.4 Hz, 1H), 4.14 and 3.90 (2 x d, J = 8.4 and 6.3 Hz, 1H), 2.93-2.58 (m, 8H), 2.54 (s, 3H), 2.21 and 2.20 (2 x d, J_{AB} = 12.3 and 12.6 Hz, 1H), 2.03 (d, J_{AB} = 12.6 Hz, 1H), 1.45 and 1.42 (2 x d, J = 7.5 and 7.2 Hz, 3H), 0.97-0.87 (m, 18H); FAB MS m/z: 558 (MH^+); HRMS calcd for $C_{29}H_{44}N_5O_6$ (MH^+) 558.3292, found: 558.3307; Anal ($C_{29}H_{43}N_5O_6 \cdot \frac{1}{2}H_2O$) C, H, N.

Example 53.
***N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(methylcarbamoyl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (86, Table 6).** This compound was prepared according to the alternative procedure for the preparation of α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 100%, (system D) 98%; IR (KBr) υ 3320, 1645 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.61 and 8.56 (2 x m, 1H), 8.18-8.05 (m, 1H), 7.97 and 7.93 (2 x d, *J* = 6.4 and 6.3 Hz, 1H), 7.60 (br d, *J* = 7.3 Hz, 1H), 5.03-4.90 (m, 1H), 4.65-4.50 (m, 1H), 4.13 and 4.12 (2 x d, *J* = 8.6 and 8.6 Hz, 1H), 2.94 (br s, 3H), 2.80 and 2.79 (2 x s, 3H), 2.71-2.55 (m, 5H), 2.20 (d, *J* = 12.4 Hz, 1H), 2.04 and 2.01 (2 x d, *J* = 12.7 and 12.7 Hz, 1H), 1.23 and 1.22 (2 x d, *J* = 7.3 and 7.0 Hz, 3H), 0.95 (s, 9H), 0.91 (br s, 9H); FAB MS m/z: 484.3 (MH^+), 506.3 (M + 23); HRMS calcd for $C_{23}H_{42}N_5O_6$ (MH^+) 484.3135, found: 484.3148.

Example 54.
***N*1-[2-(dimethylcarbamoyl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide.** This compound was prepared according to the procedure for α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 99%, (system D) 99%; IR (KBr) 3302 , 1719, 1644 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.27 and 8.16 (2 x d, *J* = 6.4 and 6.7 Hz, 1H), 8.11 and 8.06 (2 x d, *J* = 7.6 and 7.9 Hz, 1H), 7.59 and 7.58 (2 x d, *J* = 8.6 and 8.0 Hz, 1H), 4.62-4.50 (m, 2H), 4.13 and 4.12 (2 x d, *J* = 8.0 and

8.6 Hz, 1H), 2.94 (br s, 3H), 2.86 and 2.85 (2 x s, 6H), 2.80 (s, 3H), 2.72-2.56 (m, 2H), 2.23-2.16 (2 x d, *J* = 12.7 and 12.7 Hz, 1H), 2.10-1.90 (m, 1H), 1.30 and 1.29 (2 x d, *J* = 7.3 and 7.3 Hz, 3H), 0.95 (s, 9H), 0.90 (s, 9H); FAB MS m/z: 498.3 (MH^+), 520.3 (M + 23); HRMS calcd for $C_{24}H_{44}N_5O_6$ (MH^+) 498.3292, found: 498.3309.

Example 55.

***N*1-(2-[2-(benzyloxy)ethyl]carbamoyl-1-methyl-2-oxoethyl)-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (88, Table 6).** This compound was prepared according to the procedure for α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 97%, (system D) 95%; IR (KBr) υ 3299, 1645, 1527 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 8.67 and 8.62 (2 x t, *J* = 5.7 Hz, 1H), 8.15 and 8.10 (2 x d, *J* = 7.5 and 6.3 Hz, 1H), 7.98 and 7.93 (2 x d, *J* = 6.3 and 6.3 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.40-7.20 (m, 5H), 5.0-4.90 (m, 1H), 4.65-4.55 (m, 1H), 4.47 (s, 2H), 4.13 and 4.12 (2 x d, *J* = 8.7 and 8.4 Hz, 1H), 3.51 (t, *J* = 6 Hz, 2H), 3.37-3.30 (m, 2H), 2.94 and 2.93 (2 x s, 3H), 2.80 and 2.79 (2 x s, 3H), 2.75-2.60 (m, 2H), 2.20 (d, *J* = 12.6 Hz, 1H), 2.04 and 2.02 (2 x d, *J* = 12.6 and 12.6 Hz, 1H), 1.23 and 1.22 (2 x d, *J* = 7.2 and 7.2 Hz, 3H), 0.95 (s, 9H), 0.91 (s, 9H); FAB MS m/z: 604 (MH^+), 626 (M + 23); HRMS calcd for $C_{31}H_{50}N_5O_7$ (MH^+) 604.3710, found: 604.3690.

Example 56.

***N*1-2-[(1,3-benzodioxol-5-ylmethyl)carbamoyl]-1-methyl-2-oxoethyl-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-**

(neopentylcarboxamido)propyl]carboxamido}butanediamide (89, Table 6). This compound was prepared according to the procedure for the preparation of α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 99%, (system D) 100%; IR (KBr) υ 3302, 1644 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.14 and 9.09 (2 x t, *J* = 6.4 and 6.1 Hz, 1H), 8.13 and 8.08 (2 x d, *J* = 7.5 and 7.5 Hz, 1H), 8.01 and 7.96 (2 x d, *J* = 6.6 and 6.0 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 6.85-6.80 (m, 2H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.97 (s, 2H), 5.02-4.86 (m, 1H), 4.65-4.51 (m, 1H), 4.31-4.08 (m, 3H), 2.92 (br s, 3H), 2.80 and 2.79 (2 x s, 3H), 2.74-2.58 (m, 2H), 2.19 (br d, *J* = 12.6 Hz, 1H), 2.03 and 2.02 (2 x d, *J* = 12.9 and 12.6 Hz, 1H), 1.23 (m, 3H), 0.94 and 0.90 (2 x s, 18H); FAB MS m/z: 604 (MH^+), 626 (M + 23); HRMS calcd for $C_{30}H_{46}N_5O_8$ (MH^+) 604.3347, found: 604.3333.

Example 57.

***N*1-2-[(1*H*-benzo[*d*]imidazol-2-ylmethyl)carbamoyl]-1-methyl-2-oxoethyl-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (90, Table 6).** This compound was prepared according to the procedure for α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 93%, (system D) 87%, IR (KBr) υ 3294, 1663, 1522 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.41 and 9.35 (2 x t, *J* = 10.8 and 10.5 Hz, 1H), 8.64 (m, 0.5H), 8.18 and 8.09 (2 x t, *J* = 14.3 and 15.2 Hz, 2H), 7.99 (d, *J* = 6.4 Hz, 0.5H), 7.78-7.52 (m, 3H), 7.48-7.34 (m, 2H), 6.48-6.20 (br d, 1H), 5.08-4.93 (m, 1H), 4.78-4.51 (m, 3H), 4.20-4.05 (m, 1H), 2.96, 2.93, 2.92 and 2.90 (4 x s, 3H), 2.80, 2.79, 2.76, and 2.72 (4 x

s, 3H), 2.71-2.55 (m, 2H), 2.20 and 2.17 (2 x d, J = 12.4 and 9.8 Hz, 1H), 2.03 and 2.02 (2 x d, J = 12.7 and 12.7 Hz, 1H), 1.28 and 1.275 (2 x d, J = 7.3 and 7.3 Hz, 2H), 0.95 (s, 9H), 0.94-0.84 (m, 9H); FAB MS m/z: 600.6 (MH^+), 618.6 (M + 19); HRMS calcd for $C_{30}H_{46}N_7O_6$ (MH^+) 600.3509, found: 600.3488.

Example 58.

***N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*S*)-1-phenylethyl]carbamoylethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (91, Table 6).** This compound was prepared according to the procedure for α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 99%, (system D) 98%; IR (KBr) υ 3300, 1647 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 9.11 and 9.07 (2 x d, J = 8.6 and 8.6 Hz, 1H), 8.12 and 8.09 (2 x d, J = 7.9 and 7.3 Hz, 1H), 8.01 and 7.93 (2 x d, J = 6.4 and 6.3 Hz, 1H), 7.60 (m, 1H), 7.37-7.17 (m, 5H), 5.01-4.86 (m, 2H), 4.67-4.51 (m, 1H), 4.14 and 4.13 (2 x d, J = 8.6 and 8.6 Hz, 1H), 2.93 and 2.92 (2 x s, 3H), 2.79 (br s, 3H), 2.73-2.54 (m, 2H), 2.19 (d, J = 12.7 Hz, 1H), 2.06 and 2.01 (2 x d, J = 8.3 and 8.3 Hz, 1H), 1.44-1.37 (m, 3H), 1.24 and 1.17 (2 x d, J = 7.6 and 7.3 Hz, 3H), 0.94 (s, 9H), 0.91 and 0.90 (2 x s, 9H); FAB MS m/z: 574.4 (MH^+), 596.3 (M + 23); HRMS calcd for $C_{30}H_{48}N_5O_6$ (MH^+) 574.3605, found: 574.3586.

Example 59.

***N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*R*)-1-phenylethyl]carbamoylethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}**

butanediamide (92, Table 6). This compound was prepared according to the procedure for α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 99%, (system D) 97%; IR (KBr) υ 3288, 1645, 1525 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.11 and 9.05 (2 x d, *J* = 8.3 and 8.6 Hz, 1H), 8.13 and 8.07 (2 x d, *J* = 7.3 and 7.6 Hz, 1H), 8.00 and 7.95 (2 x d, *J* = 6.4 and 6.4 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.37-7.18 (m, 5H), 5.02-4.84 (m, 2H), 4.63-4.51 (m, 1H), 4.14 and 4.12 (2 x d, *J* = 8.6 and 8.6 Hz, 1H), 2.91 and 2.87 (2 x s, 3H), 2.80 and 2.77 (2 x s, 3H), 2.73 and 2.53 (m, 2H), 2.19 and 2.18 (2 x d, *J* = 12.7 and 12.4 Hz, 1H), 2.09-1.98 (m, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.23 and 1.19 (2 x d, *J* = 7.3 and 7.0 Hz, 3H), 0.95 (br s, 9H), 0.91 and 0.90 (2 x s, 9H); FAB MS m/z: 574.4 (MH^+), 596.3 (M + 23); HRMS calcd for $C_{30}H_{48}N_5O_6$ (MH^+) 574.3605, found: 574.3591.

Example 60.

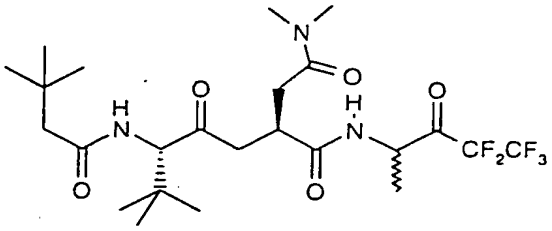
***N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*R*)-1-phenylpropyl]carbamoyl-ethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (93, Table 6).** This compound was prepared according to the procedure for α-ketoamides (Example 2). Final purification was performed by preparative HPLC. HPLC (system C) 100%, (system D) 96%; IR (KBr) υ 3297, 1647 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.07 and 9.02 (2 x d, *J* = 8.6 and 8.9 Hz, 1H), 8.13 and 8.06 (2 x d, *J* = 7.7 and 7.2 Hz, 1H), 7.99 and 7.94 (2 x d, *J* = 5.9 and 5.9 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.40-7.18 (m, 5H), 4.98-4.84 (m, 1H), 4.75-4.65 (m, 1H), 4.63-4.55 (m, 1H), 4.13 (2 x d, *J* = 8.4 and 8.4 Hz,

1H), 2.92 and 2.88 (2 x s, 3H), 2.80 and 2.77 (2 x s, 3H), 2.75-2.58 (m, 2H), 2.19 and 2.18 (2 x d, J = 12.6 and 12.6 Hz, 1H), 2.03 and 2.02 (2 x d, J = 12.6 and 12.3 Hz, 1H), 1.87-1.69 (m, 2H), 1.23 and 1.17 (2 x d, J = 7.2 and 7.2 Hz, 3H), 0.95 and 0.94 (2 x s, 9H), 0.91 and 0.90 (2 x s, 9H), 0.87-0.78 (m, 3H); FAB MS m/z: 588.7 (MH^+), 610.7 (M + 23); HRMS calcd for $C_{31}H_{50}N_5O_6$ (MH^+) 588.3761, found: 588.3744; Anal ($C_{31}H_{49}N_5O_6 \cdot H_2O$) C, H, N.

Example 61

Compounds **94** to **98** from **Table 7** and **305**, **309** and **310** from **Table 8** were synthesized according to route (b), Scheme 5. Compounds **301** to **303** and **306** to **308** from **Table 8** were synthesized according to the procedure of example 43. Compound **304** was synthesized according to the procedure of example 45.

Compound **312** was synthesized in the following manner:



312

N^4,N^4-Dimethyl-N^1-[1-(*R/S*)-methyl-2-oxo-3,3,4,4,4-pentafluorobutyl]-(2*S*)-2-{3-[(3,3-dimethyl-1-oxobutyl)-amino]-4,4-dimethyl-2-oxopentyl}-butanediamide.

A solution of ketomethylene intermediate (2.42g, 5.24 mmol, benzyl 6,6-dimethyl-(2*S*)-2-(2-dimethylamino-2-

oxoethyl)-(5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-oxoheptanoate prepared according to Moss et al., (J. Med. Chem., 1996, *39*, 4173-4180) in 4N HCl/dioxane (30 mL) was stirred at ambient temperature for 1.5 h. After removal of the solvent, the residue was co-evaporated twice with CH_3CN then dissolved in CH_3CN (50 mL) followed by the addition of *i*-PrNEt (2.74 mL, 15.72 mmol), *tert*-butyl acetic acid (0.67 ml, 5.24 mmol) and TBTU (1.70 g, 5.29 mmol). After stirring overnight at room temperature, the solvent was evaporated to dryness. The residue was dissolved in EtOAc and the solution washed sequentially with 10% aq. HCl, sat. $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Evaporation of the solvent to dryness gave the desired amide derivative as a brown gummy residue [2.41 g, FAB MS, m/z: 461(MH^+), 483$(M+Na)^+$]. The crude amide was dissolved in EtOH and the solution stirred at room temperature in the presence of 10% Pd/C (250 mg) under an atmosphere of H_2 for 18 h. After filtration of the catalyst and evaporation of the solvent to dryness, the oily residue [(1.90g, FAB MS, m/z: 399 (MH^+) corresponding to the ethyl ester derivative] was dissolved in a 1:1 mixture of MeOH-water (75 mL) and solid NaOH (758 mg) was added. The solution was stirred for 3 h at room temperature and the solvent was evaporated to dryness. The residue was dissolved in water, the solution acidified to pH 2 with 10% aq. HCl, extracted with EtOAc and the combined organic layers were washed with brine. Evaporation of the solvent to dryness gave the desired acid as a white foam [1.36g, FAB MS, m/z: 371$(MH)^+$ for. $C_{19}H_{34}N_2O_5$].

To a solution of the crude acid (370 mg) in CH_3CN (50 mL) was added (3*R/S*, 4*R/S*)-4-amino-1,1,1,2,2-pentafluoro-3-pentanol•HCl salt (229 mg, 1 mmol), TBTU (337 mg, 1.05 mmol), *i*-Pr_2NEt (0.70 ml, 4 mmol) and the mixture was stirred at room temperature for 3 h. After evaporation of the solvent to dryness, the residue was dissolved in EtOAc and the solution washed sequentially with 10% aq. HCl, aq. $NaHCO_3$ and brine. The solvent was evaporated to dryness to give the desired product (455 mg, 82% yield). FAB MS, m/z: 546 $(MH)^+$ for $C_{24}H_{40}N_3O_5F_5$.

A cold solution of the crude hydroxytriamide product (454 mg, 0.81 mmol) in EtOAc was oxidized using the Dess-Martin periodinane (0.69 g, 1.63 mmol). After the usual isolation procedure, the crude product (398 mg) was purified by flash chromatography using a 4:1 EtOAc-hexane mixture to give the title compound (128 mg). FAB MS, m/z: 544.4 (MH^+), 562.4 $(M^+H_2O)^+$ for $C_{24}H_{38}N_3O_5F_5$.

Example 62

Solid phase synthesis of activated ketones:

As shown in the following table, the peptidyl trifluoromethyl ketones and α-ketoamides of a wide chemical diversity were obtained in 12%-37% overall yield from the corresponding starting resin **103** described in Example 1. The crude material, which typically showed an homogeneity of 60-80% by reversed phase HPLC could easily be purified by semi-preparative HPLC. Since the trifluoromethyl ketone and α-ketoamide fragments **109** were racemic, the desired inhibitors were usually isolated as a 1:1 mixture of diastereomers. In

some cases each isomer could be separated during the purification but in most cases, the inhibitors were subjected to biological testing as a mixture of isomers at the activated ketone center.

Specifically, compound **218** was synthesized in the following manner:

This compound was prepared on solid phase using the semicarbazone-derived resin (**103 X'= C(O)NH-Bn**). The solid-phase synthesis as well as the cleavage condition is identical to the one reported in example 1. Yield: 33%; HPLC (phosphate): 81%; ^{1}H-NMR (400 MHz, DMSO-d_6), δ 9.18 (t, J=6.4 Hz, 1 H), 9.14 (s, 1 H), 8.39-8.26 (m, 1 H), 8.08-7.89 (m, 3 H), 7.75 (t, J=9.5 Hz, 1 H), 7.60 (broad s, 3 H), 7.34-7.22 (m, 6 H), 6.99 (d, J=8.3 Hz, 2 H), 6.61 (d, J=8.6 Hz, 2 H), 6.33-6.22 (m, 0.7 H), 4.98-4.94 (m, 2 H), 4.49-4.43 (m, 1 H), 4.33-4.00 (m, 6 H), 3.48 (t, J=5.8 Hz, 2 H), 2.96-2.91 (m, 1 H), 2.74-2.66 (m, 2 H), 2.05-1.90 (m, 1 H), 1.83 (s, 3 H), 1.65-1.45 (m, 4 H), 1.35-1.24 (m, 1 H), 1.26 (t, J=6.4 Hz, 2 H), 0.98-0.93 (m, 1 H), 0.86-0.82 (m, 6 H); FAB-MS (ES^+) calc for $C_{36}H_{52}N_7O_9$: 726; found: 726.

The IC_{50} of compound **218** was found to be 9.4 μM.

Cpd #	Sequence	Overall yield(%)
201	Val-Phe-Ser(O-t-Bu)-Asp-Ala(d,l)-CF_3	22
202	Val-Phe-Ser(O-t-Bu)-Asp(O-t-Bu)Ala(d,l)-CF_3	14
203	Ac-Asn-Asp(O-Bn)-Leu-Ala(d,l)-CF_3	40
204	Ph-C(O)Glu-Tyr-Gly-Leu-Ala(d,l)-CF_3	68
205	Ac-Phe-Leu-His-Thr-Ala(d,l)-CF_3	19
206	Ac-Phe-Leu-His-Thr-(O-tBu)Ala(d,l)-CF_3	6
207	Ac-Gly-Val-Val-Asn-Ala(d,l)-CF_3	30
208	Ac-Asp-Glu-Met-Glu-Glu-Abu(d,l)-CF_3	36
209	Boc-Gly-Phe-Leu-Abu(d,l)-CF_3	23
210	Boc-Val-Ser(O-Bn)-Gly-Asp(O-Bn)-Abu(d,l)-CF_3	29
211	Asp(O-Bn)-Ala-Pro-Abu(d,l)-CF_3	40
212	Boc-Ala-Ala-Pro-Val(d,l)-CF_3	33
213	Ph-CH_2-C(O)-Tyr-Ala-Lys-Val(d,l)-CF_3	21
214	Ac-Leu-Gly-Asp(O-Bn)-Ala-Val(d,l)-CF_3	18
215	Ac-Gly-Ser(O-Bn)-Leu-Asp(O-Bn)-Val(d,l)-CF_3	18
216	Ac-Phe-Val-Pro-Val(d or l)-CF_3	8
217	Ac-Phe-Val-Pro-Val(d or l)-CF_3	11
218	Ac-Ser-Tyr-Val-Lys-Ala(d,l)-C(O)-NH-CH_2-Ph	33
219	Ac-Asn-Asp(OBn)-Leu-Ala(d,l)-C(O)-NH-CH_2-Ph	40

Example 63.

ENZYMATIC ASSAYS.

Material & Methods: Fluorescence measurements were recorded on a Perkin-Elmer LS-50B spectrofluorimeter equipped with a plate reader accessory. UV measurements were recorded on a Thermomax microplate reader from Molecular Devices. All specificity enzymes and their respective substrates were commercially available from the following suppliers: Boehringer Mannheim (Bovine pancreas α-chymotrypsin #103314 lot 13724423-58,

porcine pancreas elastase #1027891 lot 83260521-23), Calbiochem (Human neutrophil elastase #324681 lot B12778, Human liver cathepsin B #219364 lot B14649, Succ-AAA-pNA #573459 Lot 510008), Sigma Chemical Co. (Succ-AAPF-pNA #S7388 lot 31H5805, Bachem (Z-FR-pNA #L-1242 lot 502774, Succ-AAV-pNA #L-1405, lot 116699).

HCMV N_o protease assay: HCMV N_o protease was assayed with an internally quenched fluorogenic substrate based on the maturation cleavage site (Abz-VVNASSRLY(3-NO_2)R-OH, k_{cat}/K_M = 260 $M^{-1}s^{-1}$). The fluorescence increase upon cleavage of the Ala-Ser amide bond was monitored using excitation λ = 312 nm (slit 2.5 nm) and emission λ = 415 nm (slit 5 nm). A protocol adaptable to a 96-well plate format was designed for the determination of IC_{50} values of inhibitors. Briefly, 125 nM HCMV N_o protease was pre-incubated for 5 hr at 30 °C with a range of sequentially diluted inhibitor concentrations (300 to 0.06 µM depending on the potency of each compound). After this period, enzymatic hydrolysis was initiated by addition of the fluorogenic substrate and the reaction was performed for 2 hr at 30 °C (≈30% conversion). No quenching was required before fluorescence measurement since the total scanning time by the plate reader accessory was brief relative to the duration of the reaction. The incubation buffer (essentially similar to the pre-incubation buffer) contained 50 mM Tris/HCl pH 8, 0.5M Na_2SO_4, 50 mM NaCl, 0.1 mM EDTA, 1 mM TCEP, 3% v/v DMSO and 0.05% w/v Casein. The final concentrations of HCMV N_o protease (expressed in terms of total monomer concentration) and substrate were 100 nM and 5 µM respectively. IC_{50} values were obtained through fitting of the inhibition curve to a competitive inhibition model using SAS NLIN

procedure. The mode of inhibition was determined by measurements of the initial rates (in cuvettes) at various substrate (Abz-Tbg-Tbg-Asn(Me)$_2$-Ala-SSRLY(3-NO_2)R-OH) and inhibitor concentrations using the same conditions as above. Data was plotted according to the Cornish-Bowden method ([S]/v *versus* [I]) and Dixon method (1/v *versus* [I]) to visually assess the type of inhibition (Cornish-Bowden, A. A simple graphical method for determining the inhibition constants of mixed, uncompetitive and non-competitive inhibitors. *Biochem. J.* . 1974, *137*, 143-144).

Specificity assays: The specificity of the compounds was determined against a variety of serine proteases (Human leukocyte and porcine pancreatic elastases (HLE & PPE), bovine pancreas α-chymotrypsin) and one cysteine protease (Human liver cathepsin B). In all cases a 96-well plate format protocol using a colorimetric p-nitroanilide (pNA) substrate specific for each enzyme was used. Each assay included a 1 hr pre-incubation enzyme-inhibitor at 30 °C followed by addition of substrate and hydrolysis to ≈30% conversion as measured by scanning on a UV Thermomax microplate reader. Substrate concentrations were kept as low as possible compared to K_M to reduce substrate competition. Compound concentrations varied from 300 to 0.06 μM depending on their potency. The final conditions for each assay were as followed: 50 mM Tris/HCl pH 8, 0.5 M Na_2SO_4, 50 mM NaCl, 0.1 mM EDTA, 3% DMSO, 0.01% Tween-20 with [100 μM Succ-AAPF-pNA and 250 pM α-chymotrypsin], [133 μM Succ-AAA-pNA and 8 nM porcine elastase], or [133 μM Succ-AAV-pNA and 8 nM leukocyte elastase]. 100 mM NaH_2PO_4 pH 6, 0.1 mM EDTA, 3% DMSO, 1 mM TCEP, 0.01%

Tween-20, 30 µM Z-FR-pNA and 5 nM cathepsin B (the stock enzyme was activated in buffer containing 20 mM TCEP before use).

Example 64.

Biological data.

Table 1

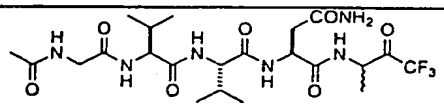
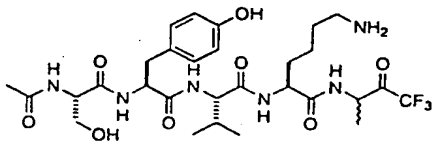
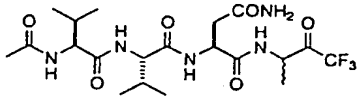
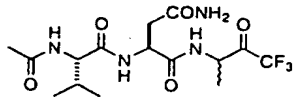
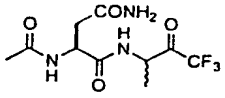
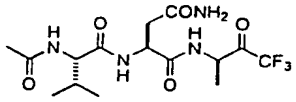
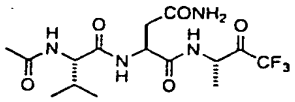
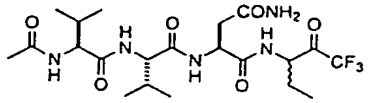
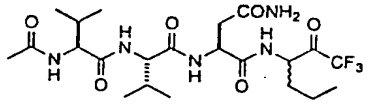
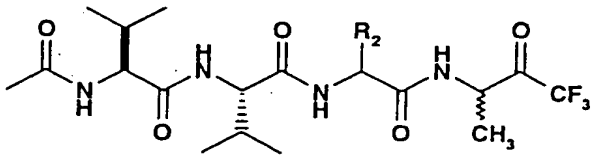
Compound	Structure	IC_{50} (μM)
37		1.8±0.3
38		2.6 ±0.4
39		3.0 ±0.3
40		80 ±15
41		>300
42		>300
43		37 ±4
44		9 ±2
45		>300

Table 2.



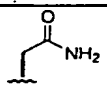
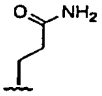
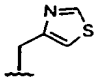
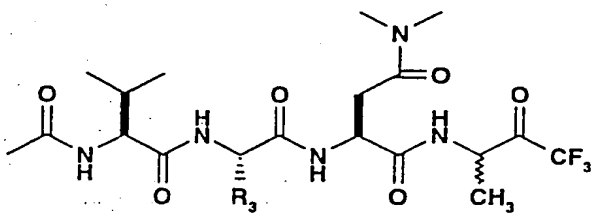
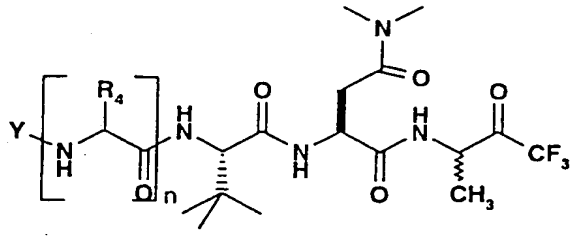
Compound	R_2	IC_{50} (μM)
39		3.0 ±0.3
46		9 ±3
47		24 ±5
48		52 ±6
49		19 ±3
50		6 ±1
51		2.0 ±0.3
52		11 ±2
53		5 ±1
54		61 ±8
55		83 ±15
56		>300

Table 3.



Compound	R_3	IC_{50} (μM)
51		2.0 ±0.3
57		4.4 ±0.5
58		1.1 ±0.2
59		3.6 ±0.5
60		6 ±1
61		15 ±4

Table 4.



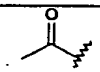
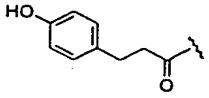
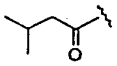
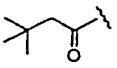
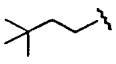
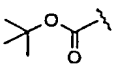
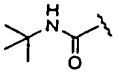
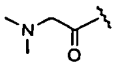
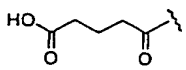
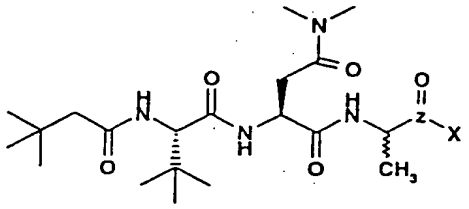
Compound	Y	n	R_4	$IC_{50}(\mu M)$
58		1		1.1 ±2
62		0	--	2.8 ±0.4
63		0	--	1.0 ±0.3
64		0	--	1.4 ±0.1
65		0	--	1.1 ±0.1
66		0	--	3.2 ±0.2
67		0	--	6 ±1
68		0	--	2.4 ±0.2
69		0	--	3.4 ±0.5
70		0	--	1.6 ±0.4

Table 5.



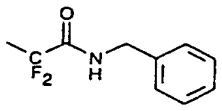
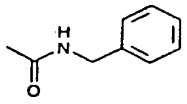
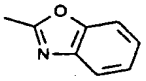
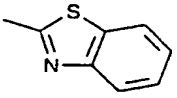
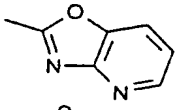
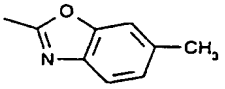
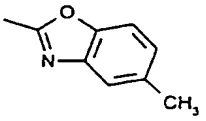
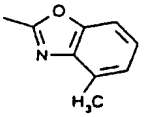
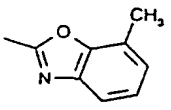
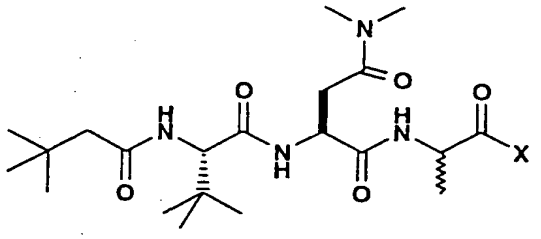
Compound	z	X	$IC_{50}(\mu M)$
65	C	CF_3	1.1 ±0.1
74	C	CF_2CF_3	0.11±0.01
75	C		0.46±0.06
76	C		0.20±0.05
77	C		0.6 ±0.1
79	P	$(OPh)_2$	0.66±0.06
80	C		1.1 ±0.3
81	C		11 ±2
82	C		0.6 ±0.1
83	C		0.6 ±0.1
84	C		0.9 ±0.2
85	C		2.8 ±0.3

Table 6.



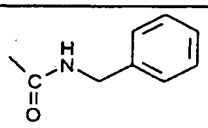
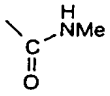
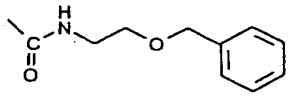
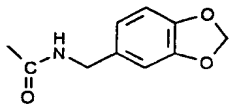
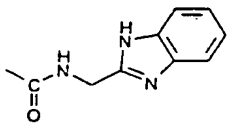
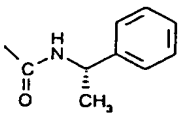
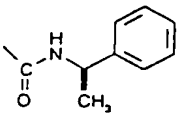
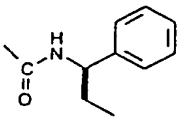
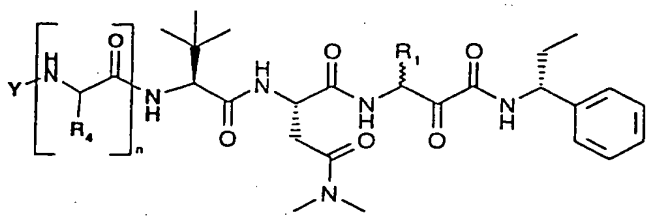
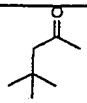
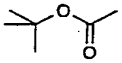
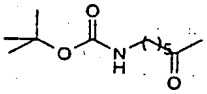
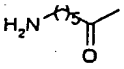
Compound	X	IC_{50} (μM)
76		0.20±0.05
86		1.1 ±0.3
88		0.14±0.03
89		0.10±0.01
90		0.21±0.05
91		3.7 ±0.8
92		0.28±0.04
93		0.11±0.03

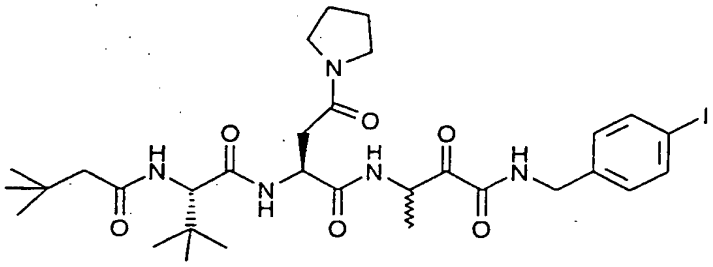
Table 7.



Cpd	Y	n	R_4	R_1	IC_{50} (μM)
93		0	--	Me	0.11
94	H	1		H	0.55
95		1		H	0.062
96		1		Me	0.057
97		1		Me	0.073

Example 65

An interesting compound related to **76** (**Table 7**), is the compound **98** (prepared according to the procedure of example 2) having the following structure:



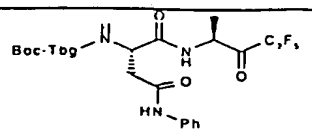
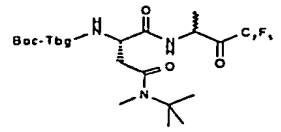
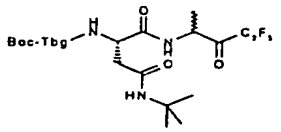
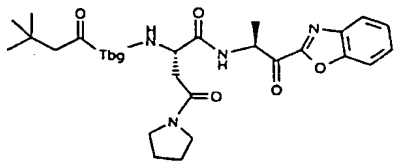
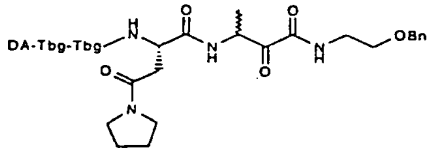
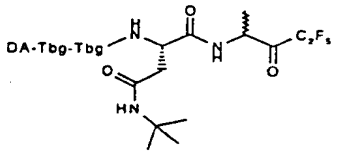
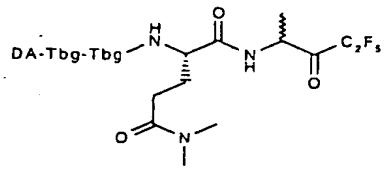
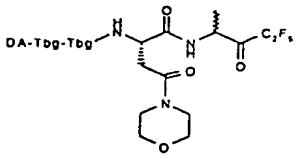
98

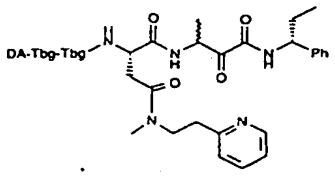
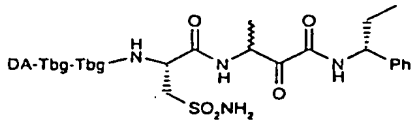
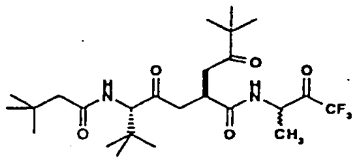
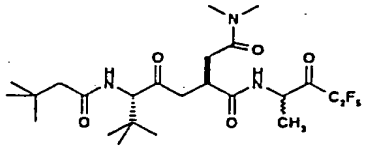
In the HCMV N_o protease assay, compound **98** had IC_{50}= 0.34 μM. The compound with its incorporated iodine atom has the added benefit of being a useful compound for X-ray crystallographic studies.

Example 66

Table 8 illustrates further compounds synthesized according to the present invention:

Table 8

Compound	Structure	IC_{50} (μM)
301		3.7
302		3.0
303		5.6
304		0.5
305		0.3
306		0.5
307		2
308		0.3

309		0.12
310		0.97
311		6.8
312		5.8

Results and Discussion.

After optimizing with the peptide portion of the inhibitors, we considered the effect of changes to the activated carbonyl group. This functionality is of particular importance for the inhibition of serine proteases because of the formation of a reversible covalent bond with the active site serine. A number of effective activated carbonyl groups have been described in the literature suitable for use with peptidomimetic inhibitors (Mehdi, S. Synthetic and naturally occurring protease inhibitors containing an electrophilic carbonyl group. *Bioorganic Chem.* 1993, *21*, 249-259). We investigated several major classes of these (Table 6). Compared with trifluoromethyl ketones, the use of pentafluoroethyl ketones, α,α-difluoro-β-ketoamides, α-ketobenzoxazoles, α-ketoamides and diphenyl phosphonates gave significant increases in activity.

Inhibitors **74** and **76** showed increases in potency by factors of ten and five respectively.

Several compounds were investigated further in order to better characterize their interactions with HCMV protease in terms of mode of inhibition. Figure 1 shows a Dixon plot obtained for compound **76** which clearly demonstrates that this compound was a competitive inhibitor of HCMV protease.

Compounds **63**, **74** and **77** gave similar results indicating that these were all inhibiting in a competitive fashion (data not shown). It is well known that the interaction of trifluoromethyl ketone-based inhibitors with serine proteases is characterized by a slow onset of inhibition. This phenomenon has been explained by the observation that trifluoromethyl ketones exist in solution almost exclusively in the hydrated form (Edwards, P.D.; Bernstein, P.R. Synthetic inhibitors of elastase. *Medicinal Research Reviews*, 1994, *14*, 128-194 and references cited therein). This produces a very low concentration of the inhibitory ketone form and results in time-dependent inhibition. As shown in Figure 2, trifluoromethyl ketone **65** exhibits slow onset of inhibition with an apparent rate constant of 5.4×10^{-3} s^{-1}.

Other carbonyl activating groups were found to be less susceptible to this slow binding behavior. Shown in Figure 3 is the progress curve obtained for compound **76**, in which equilibrium is reached more rapidly.

Compound **74** showed slow binding behavior intermediate between that of **76** and **65**, while **77** gave a progress

curve comparable to **76**. The very slow turnover rate shown by HMCV protease, coupled with slow binding kinetics for the present series of inhibitors has implications for the reliability of the enzymatic data. In order to ensure that the IC_{50} values obtained were a true reflection of inhibitory power, we utilized assay conditions in which the inhibitors were pre-incubated with the enzyme before introduction of the substrate.

Specificity: To assess specificity, we investigated the inhibitory activity of our compounds towards a variety of serine proteases. Compounds **65**, **74-85** were tested for inhibitory activity against porcine pancreatic elastase (PPE), human leukocyte elastase (HLE), bovine pancreatic α-chymotrypsin (BPC), and the cysteine protease human liver cathepsin B (cat-B) (data not shown). Compounds **65**, **74-79** all showed good specificity profiles against HLE, BPC and cat-B. Some of these compounds were weak inhibitors of PPE (which like HCMV protease shows a preference for alanine at P_1) but with specificity windows of 20 to 300 fold. One important exception to this last trend is α-ketobenzoxazole **77** which was actually seven fold *more* potent against PPE than against HCMV protease. We carried out a limited SAR of benzoxazole substitutions to try to improve the specificity profile of these compounds. Benzothiazole **80** proved to be a potent inhibitor of HCMV (IC_{50} 1.1 μM) and also interacted strongly with PPE (IC_{50} 9 μM). Compound **81** was not an inhibitor of PPE but this specificity improvement was accompanied by an 18 fold loss in activity towards HCMV protease. The various methylated benzoxazoles **82-85** were all more potent inhibitors of PPE than of HCMV protease.

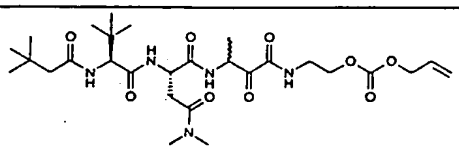
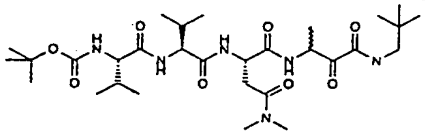
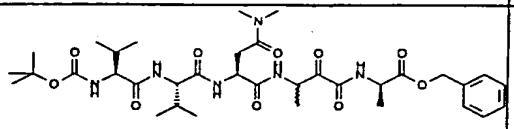
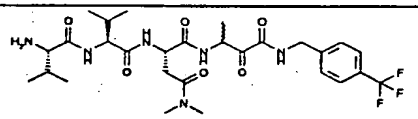
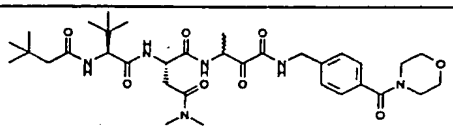
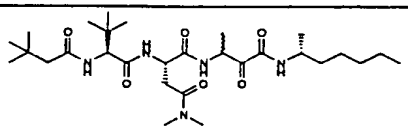
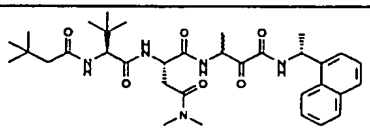
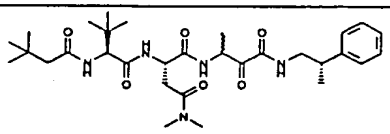
Compound **76** represented one of the most potent inhibitors of HCMV protease described so far. This structure also suggested the possibility of further increasing potency by extending the C-terminal amide moiety of this inhibitor into the S_1' binding pocket of the enzyme. The observation that the P_1' amino acids are fairly conserved (alanine or serine) prompted us to extend the C-terminus of the α-ketoamide class of inhibitors in order to try to take advantage of interactions in the S' pocket.

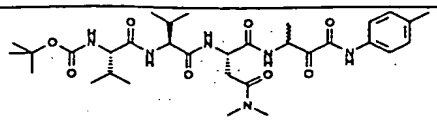
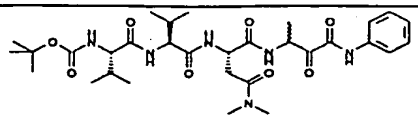
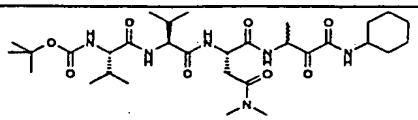
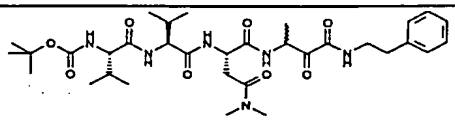
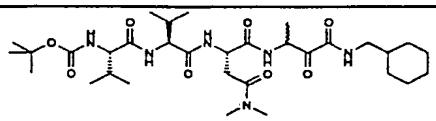
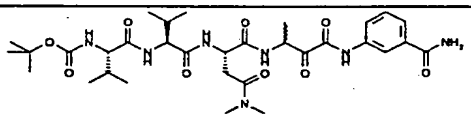
To improve the potency of compound **93** further, extension onto the P4 residue was undertaken in the glycine and alanine P1 series (**Table 7**). Since the alanine and glycine series are equipotent, the following observations can be made. Incorporating a terminal amine on the P4 residue results in a 5 fold loss in potency whereas addition of a Boc group on this amine gives a 9 fold improvement in potency. Further extensions onto the P4 residue in the form of a Boc protected 6-aminocaproyl capping group gave compound **96** which had an IC_{50} value of 75 nM. Removal of the Boc group from this inhibitor improved the potency by a factor of 2 to give compound **97** which is less than 40 nM in potency and represents the most potent compound of this series.

Table 8: compounds **301** to **312** summarize different substitutions of the P2 side-chain that gave potent inhibitors. These include various asparagine amide substitutions and a novel sulfonamide residue.

Table 9: compounds 401 to summarize different substitutions at P1'.

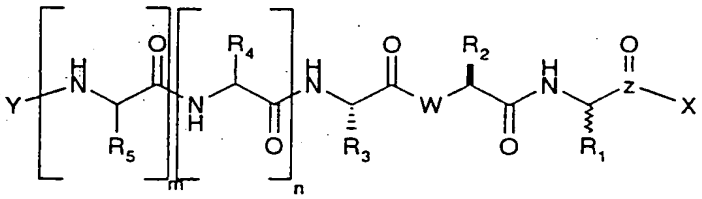
Table 9.

Cpd #	Structure	IC_{50} (μM)
401		0.59
402		4.3
403		1.6
404		1.7
405		0.5
406		0.8
407		0.2
408		0.2

409		1.4
410		1.5
411		1.8
412		0.85
413		4.4
414		1.6

What is claimed is:

1. A compound of formula I:



(I)

wherein **z** is C or P;

when **z** is C, then **X** is CF_3; C_2F_5; benzothiazole; oxazolo[4,5b]pyridine; or benzoxazole-R_7 wherein R_7 is H or methyl;
or **X** is CF_2CONH-R_6, C(O)NH-R_6,
wherein R_6 is C_{0-10} alkyl optionally substituted with phenyl or cyclohexyl, said phenyl or cyclohexyl ring being optionally substituted with Me, halogen, $-CF_3$, -CH(Me)-C(O)-OBn; $-C(O)NH_2$; or -C(O)-morpholino; said phenyl or cyclohexyl ring optionally fused with a phenyl ring;
$(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-phenyl said phenyl optionally substituted with halogen;
$(CH_2)_{1-3}$-2-benzimidazole;
$(CH_2)_{1-3}$-(3,4-methylenedioxybenzene); or
$(CH_2)_{1-3}$-O-C(O)-$OCH_2CH=CH_2$;

or, when **z** is P, then **X** is $-(OPh)_2$;

R_1 is H, Me, or Et;

R_2 is CH_2-SO_2NH_2; -C_{1-6} alkyl; -(C_{1-6} alkyl) aryl; -(C_{1-6} alkyl)thiazolo; -$CH_2C(O)$-(C_{1-6} alkyl); -$CH_2C(O)$-pyrrolidino; -$CH_2C(O)$-morpholino; -(C_{1-6} alkyl)amino; -(C_{1-6} alkyl)amido optionally mono- or di-substituted with C_{1-6} alkyl, said alkyl optionally substituted with pyridino;

W is NH, CH_2 or $CH(CH_3)$;

R_3 is -C_{1-12} alkyl; -(C_{1-6} alkyl)C(O)OH; or adamantyl;

n is 0 or 1,
R_4, when n is 1, is -C_{1-6} alkyl or -(C_{1-6} alkyl)-aryl wherein said aryl is optionally substituted with OH;

m is 0 or 1,
R_5, when m is 1, is H or -CH_2OH;

and

Y is H; $(CH_2)_2$-t-Bu; or an acyl of formula:
-C(O)-$(CH_2)_{1-6}$-C(O)OH;
-C(O)-$(CH_2)_{1-6}$-Ph wherein Ph is optionally substituted with OH;
-C(O)-$CH_2N(CH_3)_2$;
-C(O)-R_9; -C(O)O-R_9; or -C(O)NH-R_9 wherein R_9 is C_{1-6} alkyl; or
-C(O)-$(CH_2)_{1-6}$-NH_2 wherein said amino group is optionally protected with an amino protecting group.

2. A compound according to claim 1, wherein z is C;

X is CF_3;

C_2F_5;
2-benzothiazole;
2-oxazolo[4,5b]pyridine;
2-benzoxazole-R_7, wherein R_7 is H, 4-Me, 5-Me, 6-Me, or 7-Me;
CF_2CONHR_6 or $C(O)NHR_6$ wherein
R_6 is C_{1-7} alkyl, optionally substituted with cyclohexyl, naphtyl, or phenyl
optionally substituted with Me, iodo, CF_3, -CH(Me)-C(O)-OBn; $-C(O)NH_2$, or -C(O)-morpholino;
$(CH_2)_2$-O-CH_2-phenyl;
CH_2-2-benzimidazole; or
CH_2-(3,4-methylenedioxybenzene);
or
when **z** is P, then **X** is $(OPh)_2$;

R_1 is H, methyl or ethyl;

R_2 is -CH_2-phenyl;
-CH_2-(4-thiazolo);
-$(CH_2)_{1-4}$-NH_2;
-CH_2-C(O)-*tert*-butyl;
-CH_2-C(O)-(*N*-pyrrolidino);
-CH_2-C(O)-(*N*-morpholino);
-$CH_2SO_2NH_2$;
-$(CH_2)_{1-2}$-amido , the nitrogen of said amido optionally mono- or di-substituted with a substituent selected independently from: CH_3; *t*-Bu; phenyl; or -CH_2CH_2-(2-pyridino);

W is NH or CH_2;

R_3 is ethyl; isopropyl; *t*-Bu; CH_2-*t*-Bu; or adamantyl;

n is 0 or 1,
R_4, when n is 1, is isopropyl; *t*-Bu; or 4-hydroxybenzyl;

m is 0 or 1,
R_5, when m is 1, is H;

and

Y is H; $-CH_2-CH_2-t$-Bu; or an acyl of formula:
$-C(O)CH_3$;
$-C(O)CH_2-CH(CH_3)_2$;
$-C(O)CH_2-t$-Bu (DA-Tbg);
$-C(O)(CH_2)_2$-4-hydroxyphenyl;
$-C(O)-(CH_2)_3-COOH$;
$-C(O)O-t$-Bu (Boc);
$-C(O)NH-t$-Bu;
$-C(O)CH_2-N(CH_3)_2$; or
$-C(O)(CH_2)_{1-6}NH_2$, said amino group optionally protected with an amino protecting group.

3. A compound according to claim 2, wherein z is C;

X is CF_3;
C_2F_5;
benzothiazole;
benzoxazole-R_7, wherein R_7 is H, 4-Me, 5-Me, 6-Me, or 7-Me;
$-CF_2CONH-CH_2$-phenyl;
$-C(O)NHR_6$ wherein
R_6 is $-CH(Me)(CH_2)_4CH_3$; cyclohexyl; naphtyl; $-CH_2$-phenyl; $-CH(CH_3)$-phenyl; or $-CH(CH_2CH_3)$-phenyl; ; $-CH_2$-4-iodophenyl; -phenyl-CH_3;

-phenyl-CF_3; -phenyl-$C(O)NH_2$; -phenyl-C(O)-morpholino; -phenyl-CH(Me)-C(O)-OBn; -$(CH_2)_2$-O-CH_2-phenyl; -CH_2-2-benzimidazole; -CH_2-(3,4-methylenedioxybenzene); or -$(CH_2)_2$-O-C(O)-$OCH_2CH=CH_2$;

or

when **z** is P, then **X** is $(OPh)_2$;

R_1 is H or methyl;

R_2 is -CH_2-C(O)-(*N*-pyrrolidino);
-CH_2-C(O)-(*N*-morpholino);
-$CH_2SO_2NH_2$;
-$(CH_2)C(O)NH_2$;
-$(CH_2)_2C(O)N(CH_3)_2$;
-CH_2-C(O)-NH-*t*-Bu; or
-$(CH_2)_2$-C(O)-$N(CH_3)CH_2CH_2$(2-pyridino);

W is NH;

R_3 is ethyl; isopropyl; or *t*-Bu;

R_4, when **n** is 1, is isopropyl; or *t*-Bu;

R_5, when **m** is 1, is H;

and

Y is H; or an acyl of formula:
-$C(O)CH_3$;
-$C(O)CH_2$-$CH(CH_3)_2$;
-$C(O)CH_2$-*t*-Bu (DA-Tbg);
-$C(O)(CH_2)_2$-4-hydroxyphenyl;
-C(O)-$(CH_2)_3$-COOH;

-C(O)O-*t*-Bu (Boc);
-C(O)$(CH_2)_5NH_2$; or
-C(O)$(CH_2)_5$NH-Boc.

4. - A compound according to claim 3, wherein z is C;

X is C_2F_5;
-C(O)NHR_6 wherein
R_6 is -CH_2-phenyl; -CH_2-4-iodophenyl; -CH(CH_3)-phenyl; or -CH(CH_2CH_3)-phenyl; -CH(Me)-naphtyl; -CH_2CH(Me)-phenyl; -$(CH_2)_2$-O-CH_2-phenyl; -CH_2-2-benzimidazole; or -CH_2-(3,4-methylenedioxybenzene);

R_1 is H or methyl;

R_2 is -CH_2-C(O)-(*N*-pyrrolidino);
-CH_2-C(O)-(*N*-morpholino);
-$(CH_2)_2$C(O)N$(CH_3)_2$; or
-$(CH_2)_2$-C(O)-N(CH_3)CH_2CH_2(2-pyridino);

W is NH;

R_3 is isopropyl; or *t*-Bu;

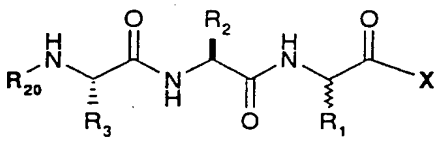
R_4, when n is 1, is *t*-Bu;

m is 0,
and

Y is an acyl of formula:
-C(O)CH_2-*t*-Bu (DA-Tbg);

-C(O)O-*t*-Bu (Boc);
-C(O)$(CH_2)_5NH_2$; or
-C(O)$(CH_2)_5$NH-Boc.

5. A compound of formula



wherein
X is CF_3, C_2F_5, 2-benzothiazole, CF_2CONHR_6, $CONHR_6$, wherein R_6 is $CH_2C_6H_5$, CH_2(4-iodophenyl), CH_3, $(CH_2)_2OCH_2C_6H_5$, CH_2-2-benzimidazole, CH_2-(3,4-methylenedioxybenzene), $CH(CH_3)C_6H_5$ or $CH(CH_2CH_3)C_6H_5$; or **X** is 2-benzoxazole-R_7 wherein R_7 is H, 4-CH_3, 5-CH_3,6-CH_3 or 7-CH_3;

R_1 is H, CH_3 or CH_2CH_3;

R_2 is CH_2CONH_2, $CH_2CH_2CONH_2$, CH_2-thiazole, $CH_2CON(CH_3)_2$, CH_2CO-(pyrrolidino), $CH_2CH(CH_3)_2$ or $CH_2C_6H_5$;

R_3 is Et, $CH(CH_3)_2$, $C(CH_3)_3$, adamantyl, $CH_2C(CH_3)_3$ or $C(CH_3)_2CO_2H$;

and

R_{20} is $COCH_2C(CH_3)_3$, $COCH_2CH_2C_6H_4OH$, $COCH_2CH(CH_3)_2$, $CO_2C(CH_3)_3$, $CONHC(CH_3)_3$, $COCH_2N(CH_3)_2$, $CO(CH_2)_3CO_2H$, CO-*(S)*-$CH(NH_2)C(CH_3)_3$, CO-*(S)*-$CH\{NHC(O)O\text{-}C(CH_3)_3\}C(CH_3)_3$, CO-*(S)*-$CH\{NHCO(CH_2)_5NHC(O)OC(CH_3)_3\}C(CH_3)_3$ or

CO-*(S)*-CH{NHCO$(CH_2)_5NH_2$}C$(CH_3)_3$.

6. A compound according to claim 1 selected from the group consisting of:

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-2-methyl-1-[((1*S*)-2-methyl-1-[(methylcarboxamido)methyl] carboxamidopropyl) carboxamido]propylcarboxamido) butanediamide (**37**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-6-amino-2-((1*S*)-1-[((1*S*)-1-[(1*S*)-2-hydroxy-1-(methylcarboxamido) ethyl]carboxamido-2-(4-hydroxyphenyl)ethyl)carboxamido]-2-methylpropyl-carboxamido)hexanamide (**38**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamidopropyl) carboxamido]butanediamide (**39**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-{(1*S*)-2-methyl-1-[(methylcarboxamido)-propyl]carboxamido}butanediamide (**40**);

*N*1-(3,3,3-trifluoro-(1*S*)-methyl-2-oxopropyl)-(2*S*)-2-{(1*S*)-2-methyl-1-[(methylcarboxamido)propyl] carboxamido}butanediamide (**43**);

*N*1-(1-ethyl-3,3,3-trifluoro-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl] carboxamidopropyl)carboxamido]butanediamide (**44**);

*N*1-(1-(3,3,3,-trifluoro-1-propyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methyl-carboxamido)propyl]carboxamidopropyl)carboxamido]butane diamide (**45**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]pentanediamide (**46**);

(3*S*)-3-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido-propyl)carboxamido]-3-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]propanoic acid (**47**);

*N*1-[(1*S*)-1-((1*S*)-2-hydroxy-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)-2-methylpropyl]-(2*S*)-3-methyl-2-(methylcarboxamido) butanamide (**48**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-6-amino-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]hexanamide (**49**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-2-(1,3-thiazol-4-yl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)-carbamoyl]ethylcarbamoyl) propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**50**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl) carboxamido]butanediamide (**51**);

*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-4-methyl-2-[((1*S*)-2-methyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl)carboxamido]pentanamide (**52**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-2-phenyl-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-ethylcarbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**53**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-2-methyl-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-propylcarbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**54**);

*N*1-[(1*S*)-2-methyl-1-((1*S*)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**55**);

*N*1-[(1*S*)-2-methyl-1-((1*R*)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]ethyl-carbamoyl)propyl]-(2*S*)-3-methyl-2-(methylcarboxamido)butanamide (**56**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropyl)carboxamido]butanediamide (**57**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-2,2-dimethyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido-propyl)carboxamido]butanediamide (**58**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-3,3-dimethyl-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido butyl)carboxamido]butanediamide (**59**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((*S*)-1-(1-adamantyl)-1-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamido methyl)carboxamido]butanediamide (**60**);

(3*S*)-3-((1*S*)-2-(dimethylcarbamoyl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl]-ethylcarbamoyl)-2,2-dimethyl-3-[(1*S*)-2-methyl-1-(methylcarboxamido)propyl]carboxamidopropanoic acid (**61**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(methylcarboxamido)propyl]carboxamidobutanediamide (**62**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-1-[(4-hydroxyphen-ethyl)carboxamido]-2,2-dimethylpropylcarboxamido) butanediamide (**63**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-1-(isobutylcarboxamido)-2,2-dimethylpropyl]carboxamidobutanediamide (**64**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propylcarboxamido]butanediamide (**65**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-((1*S*)-1-[(3,3-dimethyl-butyl)amino]-2,2-dimethylpropylcarboxamido]butanediamide (**66**);

4N,4N-Dimethyl-1N-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-2-[1-(*tert*-butoxycarbonyl-amino)-2,2-dimethyl-(1S)-propylcarboxamido]-(2S)-butanediamide (**67**);

*N*4,*N*4-Dimethyl-N1-(3,3,3-trifluoro-1-methyl-2-oxopropyl-2-[1-(tert-butylaminocarbonyl-amino)-2,2-dimethyl-(1S)-propylcarboxamido]-(2S)-butanediamide (**68**);

*N*4,*N*4-dimethyl-*N*1-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-(2*S*)-2-[((1*S*)-1-[(dimethyl-amino)methyl]carboxamido-2,2-dimethylpropyl) carboxamido]butanediamide (**69**);

4-[(1*S*)-1-((1*S*)-2-(dimethylcarbamoyl)-1-[(3,3,3-trifluoro-1-methyl-2-oxopropyl)carbamoyl] ethylcarbamoyl)-2,2-dimethylpropyl]carbamoylbutanoic acid (**70**);

*N*4,*N*4-dimethyl-*N*1-(3,3,4,4,4-pentafluoro-1-methyl-2-oxobutyl)-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentyl carboxamido)propyl]carboxamidobutanediamide (**74**);

*N*1-[3-(benzylcarbamoyl)-3,3-difluoro-1-methyl-2-oxopropyl]-*N*4,*N*4-dimethyl-(2*S*)-2-[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamidobutanediamide (**75**);

3-{2-[2-(3,3-Dimethyl-butyrylamino)-3,3-dimethyl-butyrylamino]-3-dimethylcarbamoyl-propionylamino}-2-oxo-butyric acid benzyl amide (76);

*N*1-[2-(1,3-benzoxazol-2-yl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl -1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (77);

Diphenyl *N*4,*N*4-dimethyl-*N*1-(1-aminoethylphosphinate)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butane diamide (79);.

*N*1-[2-(1,3-benzothiazol-2-yl)-1-methyl-2-oxoethyl]-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-di-methyl-1-(neopentylcarboxamido)propyl]carboxamido}butane diamide (80);

*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-[1,3]oxazolo[4,5-*b*]pyridin-2-yl-2-oxoethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (81);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(6-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (82);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(5-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (83);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(4-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (84);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(7-methyl-1,3-benzoxazol-2-yl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (85);

*N*4,*N*4-dimethyl-*N*1-[1-methyl-2-(methylcarbamoyl)-2-oxoethyl]-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (86);

*N*1-(2-[2-(benzyloxy)ethyl]carbamoyl-1-methyl-2-oxoethyl)-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (88);

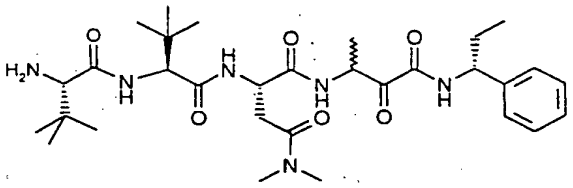
*N*1-2-[(1,3-benzodioxol-5-ylmethyl)carbamoyl]-1-methyl-2-oxoethyl-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (89);

*N*1-2-[(1*H*-benzo[*d*]imidazol-2-ylmethyl)carbamoyl]-1-methyl-2-oxoethyl-*N*4,*N*4-dimethyl-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (90);

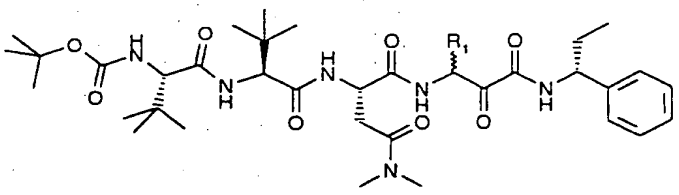
*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*S*)-1-phenylethyl]carbamoylethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido}butanediamide (91);

*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*R*)-1-phenylethyl]carbamoylethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**92**);

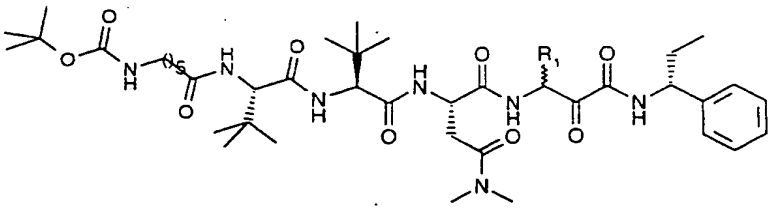
*N*4,*N*4-dimethyl-*N*1-(1-methyl-2-oxo-2-[(1*R*)-1-phenylpropyl]carbamoyl-ethyl)-(2*S*)-2-{[(1*S*)-2,2-dimethyl-1-(neopentylcarboxamido)propyl]carboxamido} butanediamide (**93**);



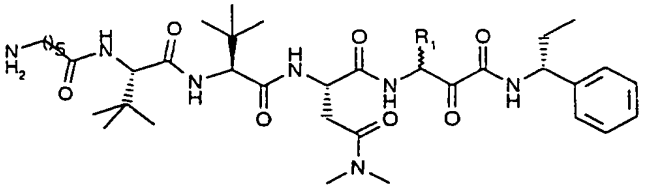
94;



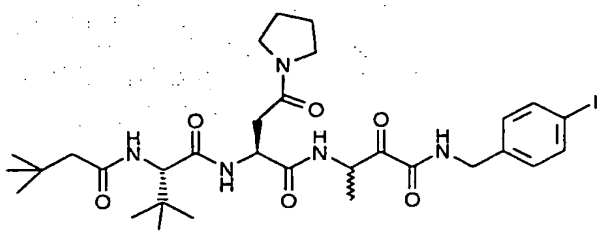
95;



96;

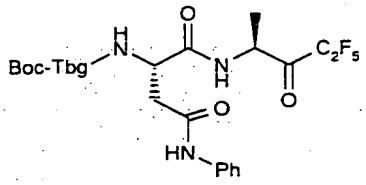


97;

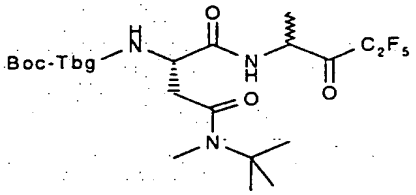


98;

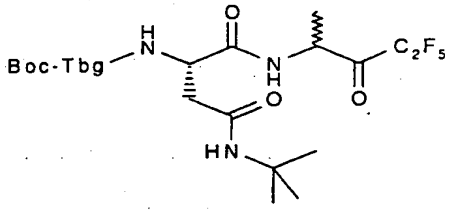
Ac-Ser-Tyr-Val-Lys-Ala(d,l)-C(O)-NH-CH_2-Ph 218;



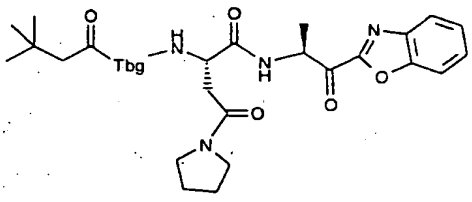
301;



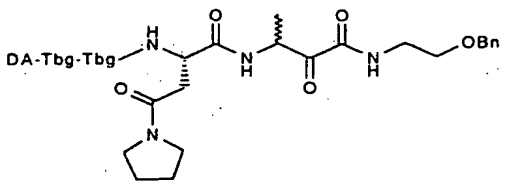
302;



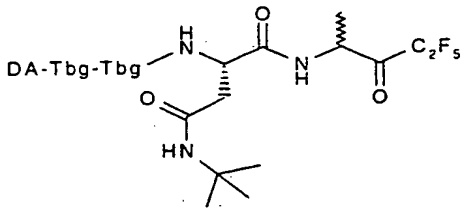
303;



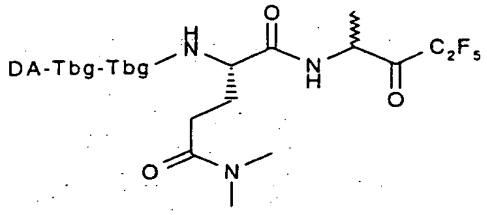
304;



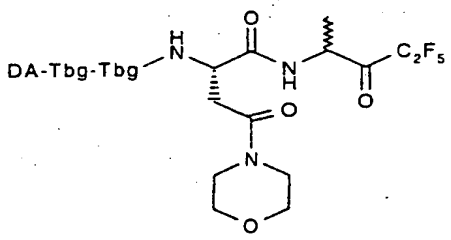
305;



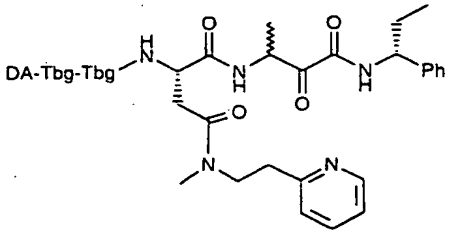
306;



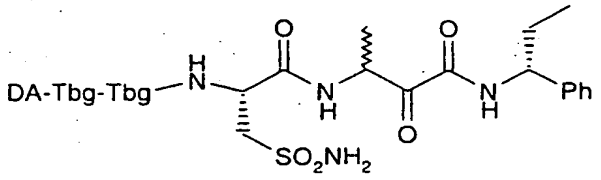
307;



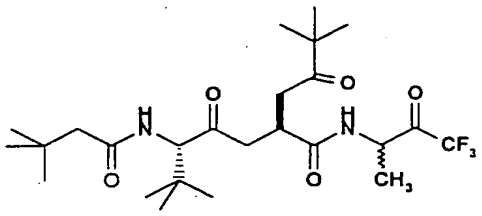
308;



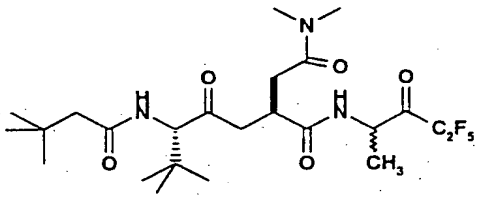
309;



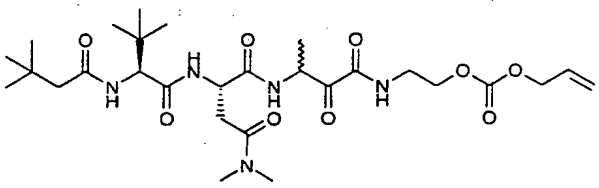
310;



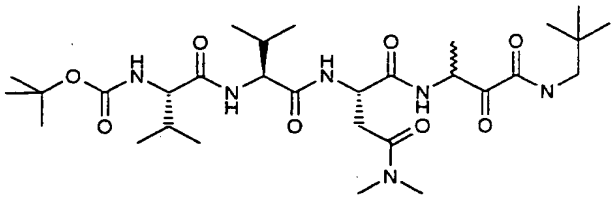
311;



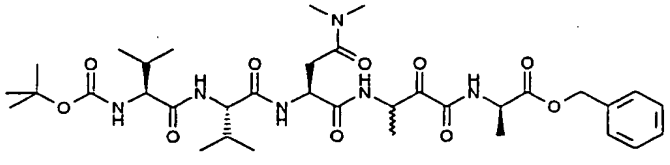
312;



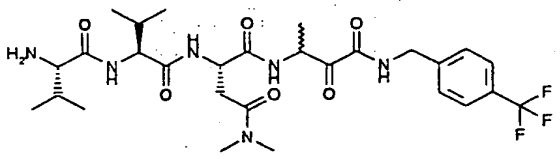
401;



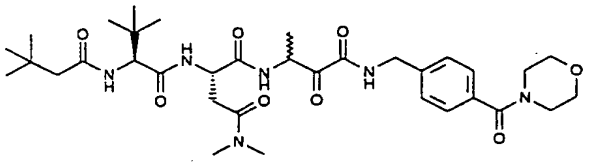
402;



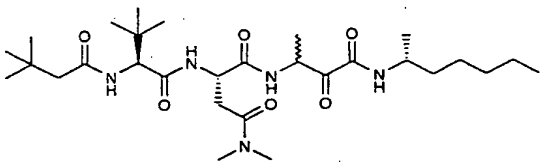
403;



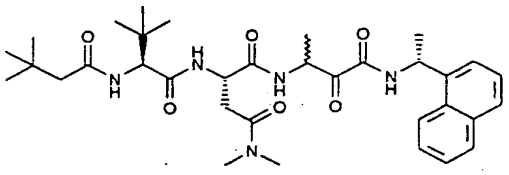
404;



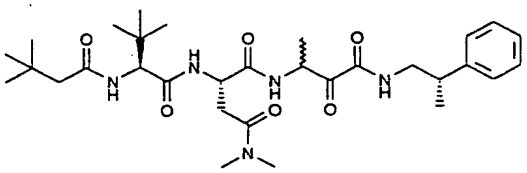
405;



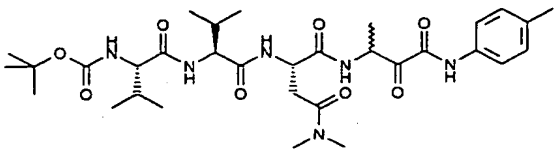
406;



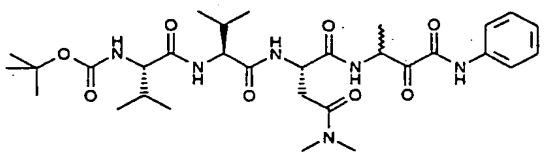
407;



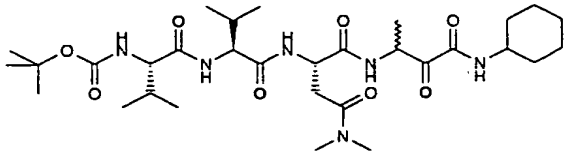
408;



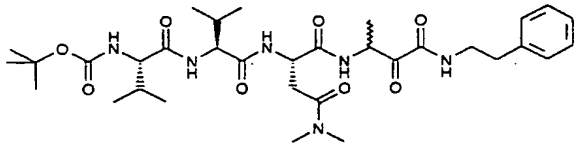
409;



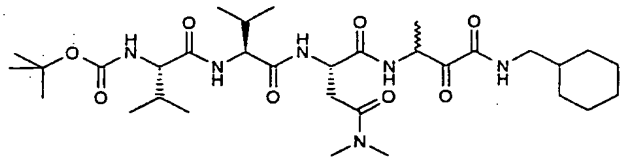
410;



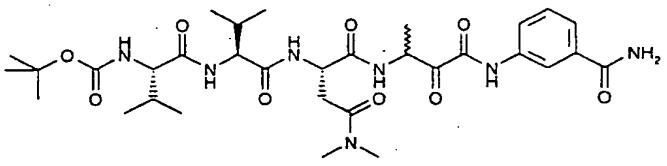
411;



412;



413; and



414.

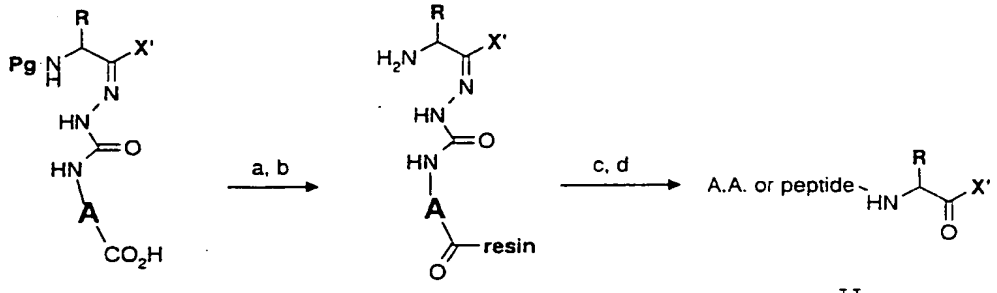
7. The compound according to claim 6, selected from the group consisting of: compound number 37, 38, 39, 44, 46, 50, 51, 53, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 74, 75, 76, 77, 79, 80, 82, 83, 84, 85, 86, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 218, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, and 401 to 414.

8. The compound according to claim 7, selected from the group consisting of: compound number 37, 51, 58, 63, 64, 65, 70, 74, 75, 76, 77, 79, 80, 82, 83, 84, 85, 86, 88, 89, 90, 92, 93, 94, 95, 96, 97, 98, 304, 305, 306, 307, 308, 309, 310, 311, 312, 401, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, and 414.

9. The compound according to claim 8, selected from the group consisting of: compound number 74, 76, 88, 89, 90, 92, 93, 95, 96, 97, 98, 305, 308, 309, 407, and 408.

10. A solid phase process for the synthesis of peptidyl activated ketones comprising the step of:

a) coupling a semicarbazone acid of formula 113 to a resin by *in situ* activation;



113 103 II

wherein R is a side chain of a natural or non-natural amino acid;

and X' is CF_3, $CF_2CONH\text{-}R_{30}$, $C(O)NH\text{-}R_{30}$, or $C(O)OR_{30}$, wherein R_{30} is a cyclic $C_{3\text{-}12}$ alkyl or acyclic $C_{1\text{-}10}$ alkyl or cyclic $C_{3\text{-}12}$ alkenyl or acyclic $C_{2\text{-}12}$

alkenyl, said alkyl or alkenyl optionally substituted with NH_2, OH, SH, halo, or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom independently selected from the group consisting of: O, S, and N; or
R_{30} is a C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl; said aryl or aralkyl optionally containing at least one heteroatom independently selected from the group consisting of: O, S, and N;

A is a divalent spacer group which comprises a non-reactive divalent hydrocarbyl group having from 2 to 15 carbon atoms;

and

Pg is an amino protecting group

b) deprotecting said amino protecting group to give the desired resin of formula **103**;

c) coupling said resin with one or more amino acid in a sequential manner by standard chemistry; and

d) cleaving said peptide from said resin to obtain a peptidyl activated ketone of formula **II**.

11. The process of claim 10, wherein said cleavage step is carried out in THF, aq.HCl, and AcOH at a temperature of about 60°C for about 4 hours; and said resin is filtered at least once.

12. The process of claim 10, wherein said resin is selected from the group consisting of: polystyrene or pegylated polystyrene functionalized with benzydrylamine (BHA); 4-methyl benzydrylamine (MBHA); and aminomethyl (AM).

13. The process of claim 10, wherein said *in situ* activation is carried out with the addition of a coupling agent selected from the group consisting of: 2-(*1H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU); 2-(*1H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU); diisopropyl carbodiimide (DIC), and dicyclohexyl carbodiimide (DCC).

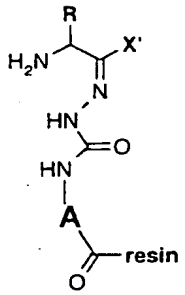
14. The process of claim 10, wherein said amino protecting group is selected from the group consisting of: *t*-butyloxycarbonyl (Boc); 9-fluorenylmethyloxy carbonyl (Fmoc); and allyloxy carbonyl (Alloc).

15. The process of claim 10, wherein **X'** is $C(O)NH_2CH_2$-phenyl or $C(O)OCH_2CH{=}CH_2$.

16. The process of claim 10, wherein **R** is selected from the group consisting of: CH_3; CH_2CH_3; $CH_2CH_2CH_3$; $(CH_2)_4NH_2$; $CH(CH_3)_2$; CH_2-phenyl; $(CH_2)_3$-NH-$CH=N(NH_2)$.

17. The process of claim 10, wherein **A** is cyclohexyl, phenyl or benzyl.

18. A resin of the formula 103:



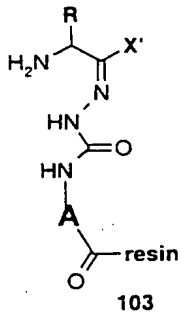
103

wherein **R**, **X'** and **A** are as defined in claim 10.

19. The resin according to claim 18, wherein said resin is selected from the group consisting of: polystyrene or pegylated polystyrene functionalized with benzydrylamine (BHA); 4-methyl benzydrylamine (MBHA); and aminomethyl (AM).

20. The resin according to claim 18, wherein A is cyclohexyl, phenyl or benzyl.

21. The use of a resin of formula 103 for the solid phase synthesis of peptidyl activated ketones:



103

wherein R, X' and A are as defined in claim 10.

22. The use of said resin according to claim 21, wherein said resin is selected from the group consisting of: polystyrene or pegylated polystyrene functionalized with benzydrylamine (BHA); 4-methyl benzydrylamine (MBHA); and aminomethyl (AM).

23. The use according to claim 21, wherein A is cylcohexyl, phenyl or benzyl.

FIGURE 1

Dixon plot for competitive inhibition of compound 76 against HCMV protease.

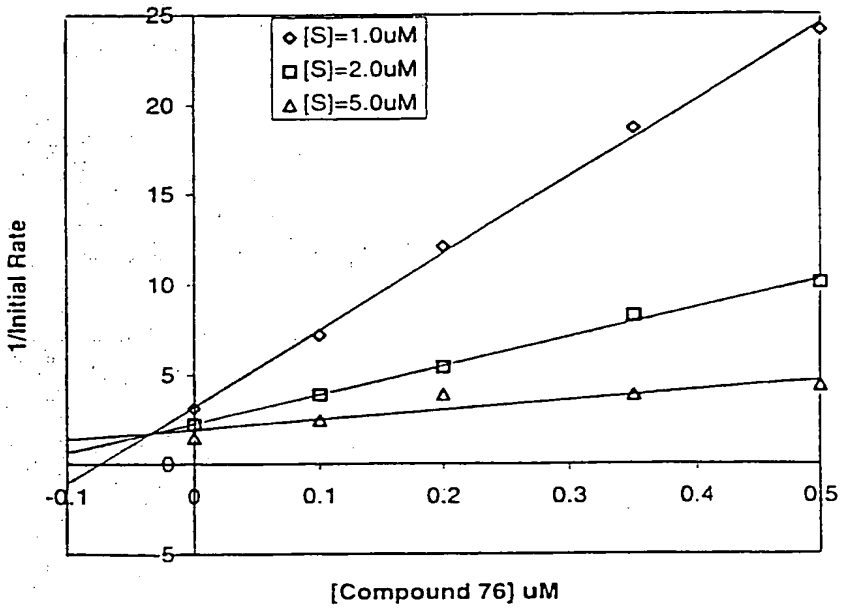


FIGURE 2

Progress curve for the inhibition of HCMV protease by compound 65.

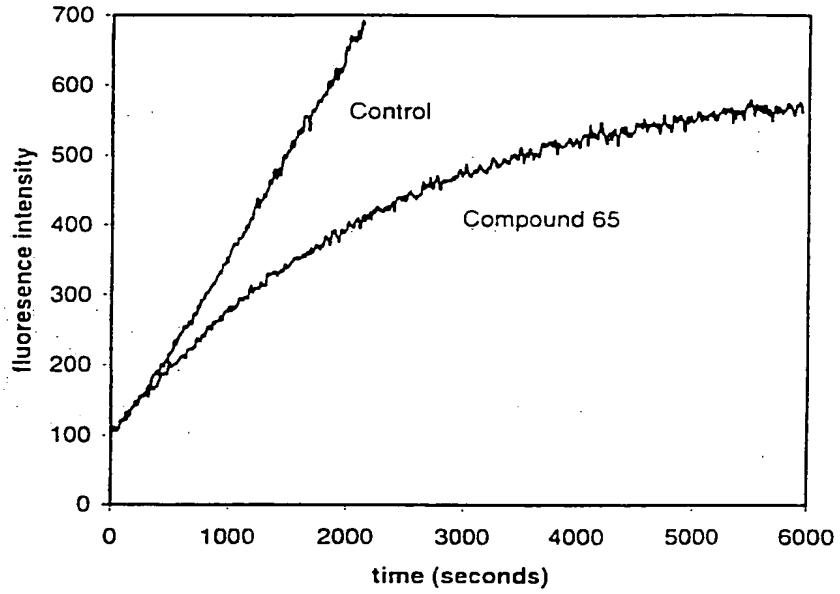
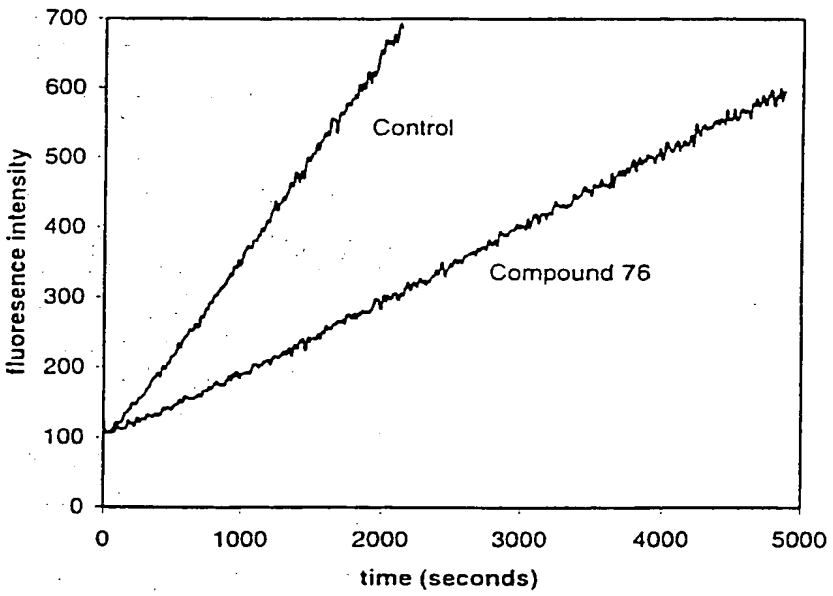


FIGURE 3

Progress curve for the inhibition of HCMV protease by compound 76.



INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 97/01004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/10 C07K5/08 C07K5/06 C07K5/02 A61K38/55

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C W DERSTINE ET AL.: "Trifluoromethyl-substituted imidazolines; novel precursors of trifluoromethyl ketones anenable to peptide synthesis " JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 118, no. 35, 4 September 1996, DC US, pages 8485-8486, XP002065952 see table 1 --- -/--	1-3,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 1998	15/06/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Masturzo, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/CA 97/01004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A H ABUELYAMAN ET AL.: "Fluorescent derivatives of diphenyl '1-(N-Peptidylamino)alkyl!phosphonate esters; synthesis and use in the inhibition and cellular localization of serine proteases." BIOCONJUGATE CHEMISTRY., vol. 5, no. 5, October 1994, WASHINGTON US, pages 400-405, XP000465951 see table 1 ---	1
X	EP 0 410 411 A (MERRELL DOW PHARMACEUTICALS INC.) 30 January 1991 see the whole document ---	1-3,5
P,X	WO 97 10231 A (CEPHALON INC.) 20 March 1997 see the whole document ---	1-3,5
A	A M MURPHY ET AL.: "Automated synthesis of peptide C-terminal aldehydes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 114, no. 8, 8 April 1992, DC US, pages 3156-3157, XP000605298 see the whole document ---	10-23
P,X	W OGILVIE ET AL. : "Peptidomimetic inhibitors of the human cytomegalovirus protease" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 25, 5 December 1997, WASHINGTON US, pages 4113-4135, XP002065953 see the whole document ---	1-9
P,X	P B BONNEAU ET AL.: "Evidence of a conformational change in the human cytomegalovirus protease upon binding of peptidyl-activated carbonyl inhibitors" BIOCHEMISTRY., vol. 36, no. 41, 14 October 1997, EASTON, PA US, pages 1264-12652, XP002065954 see the whole document -----	1-9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CA 97/01004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 410411 A	30-01-1991	AU 632836 B	14-01-1993
		AU 5974290 A	31-01-1991
		CA 2021660 A	27-01-1991
		CN 1049016 A	06-02-1991
		FI 94420 B	31-05-1995
		HU 209931 B	28-12-1994
		IL 95168 A	31-10-1995
		JP 3086852 A	11-04-1991
		PT 94811 A	20-03-1991
WO 9710231 A	20-03-1997	US 5723580 A	03-03-1998
		AU 6977096 A	01-04-1997